HEALTH CARE INDUSTRY MARKET UPDATE

Pharmaceuticals

January 10, 2003

Dear Friends of CMS:

As the regulators of over $500 billion per year of Medicare, Medicaid, and S-CHIP funds, we believe it is incumbent on us to better understand the finances of our contractors, health providers, and other related businesses that provide services to the more than 70 million beneficiaries these programs serve. Health plans, hospitals, nursing homes, home health agencies, medical device manufacturers, and pharmaceutical companies are just some of those whose finances depend heavily on these public programs.

I have always been surprised at how little Wall Street and Washington interact—and how companies often provide different financial information to each. I am a strong believer in adequate funding for our major partners in these programs, but I do not think they should be saying one thing to investors and another to regulators (as it is occasionally in their interest to do). If health plans or providers need help, we should have a thorough understanding of their real financial status to assess the true level of need. Many investment banking firms conduct detailed analyses of major health providers, both for the equity investors in for-profit companies, and for the debt holders of for-profit and nonprofit entities. Health systems typically provide these investors with clear financial data. These data can be used by regulators and legislators to assess funding adequacy or the need for regulatory reforms.

CMS' Office of Research, Development & Information (ORDI) has gathered research reports from the major investment firms, summarized their analyses, and condensed them into a short, and hopefully, understandable format. Our goal is to provide objective summary information that can be quickly used by CMS, HHS, Congress, and their staffs that oversee these programs. The primary person at CMS assigned to this task is Lambert van der Walde. Lambert previously worked for Salomon Smith Barney in New York and is experienced with corporate financial analysis and research review. Also on the team is Kristen Choi who previously worked for JPMorgan in New York in healthcare equity research.

This, our sixth report, focuses on pharmaceutical manufacturers, including branded pharmaceutical, generic pharmaceutical, and biotechnology companies. Medicare will spend over $7 billion on outpatient drugs this year—and far far more in the future if Congress passes a Medicare drug benefit. As a result, a review of the financial performance of the industry is timely. In coming months, we will continue to review the major provider and supplier sectors. Though I am proud of this effort, and believe it will add to understanding of the programs, we welcome comments on the content and format of this report. We want to make this as consumer friendly as possible for everyone who reads it. Please provide comments to Lambert van der Walde at lvanderwalde@cms.hhs.gov or Kristen Choi at kchoi@cms.hhs.gov.

Sincerely,

Tom Scully

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Wall Street's View of Pharmaceutical Manufacturers

Despite recent stock market declines, drug makers continue to remain highly profitable.

- **The branded pharmaceutical industry has faced pressure from recent generic entries on blockbuster products. The financial impact has been exacerbated by a relative lack of new product flow.**
- **Analysts project earnings growth will re-accelerate for branded drug makers in 2003.**
- **The generic drug industry has benefited from recent patent expirations for branded drugs and managed care cost-containment efforts that drive generic use.**
- **Most biotechnology companies are unprofitable, but the strong performance of a few profitable biotechs resembles that of the branded pharmaceutical industry.**
- **Intellectual property litigation and legislative and regulatory action are closely monitored by investors.**

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EXECUTIVE SUMMARY

In 2001 prescription drug spending in the U.S. totaled $141 billion, or 10% of national health expenditures. Prescription drugs are manufactured by the branded pharmaceutical, generic pharmaceutical, and biotechnology industries. Brand name drugs accounted for 92% of the sales volume but only half of the dispensed prescription volume in the United States in 2001, according to IMS Health.

Earnings growth for the branded pharmaceutical companies is expected to re-accelerate in 2003.

Average revenue growth for the branded pharmaceutical industry has slowed from 9.5% in 2001 to 4.5% for the first three quarters in 2002. Slowing revenue growth has been primarily due to a series of generic entries since mid-2001. As generics begin to compete with existing products, the need to discover new blockbusters (*i.e.*, drugs with sales over $500 million) has become especially urgent. Analysts note, however, that rising research and development (R&D) spending has not resulted in increased new product flow recently. Despite this earnings pressure, branded drug companies remain highly profitable.

The generic drug industry saw average revenue growth spike from 14% in 2000 to 55% in 2001, benefiting from patent expirations on branded drugs. Although growth has slowed in 2002, analysts consider the fundamentals of the generic drug industry to be strong. Managed care cost-containment efforts have accelerated conversion to generic from branded drugs. After generic entry, it now only takes six to eight weeks for a generic to take 50% share of dispensed prescriptions of the branded version, compared to six months historically.

Average drug industry profit margins range from 16%-24%.

Although the vast majority of biotechnology companies are unprofitable, the performance of the major profitable biotechs has begun to resemble that of the branded pharmaceutical industry. In 2001, the average profit margin was 20% for the branded pharma companies, 24% for the profitable biotechs, and 16% for the generic drug companies. Differences in business models are apparent in their expense structures. Average R&D expenses (as a percent of revenues) are highest for biotech (25%), less for branded pharma (13%) and lowest for generics (6%). Average selling, general and administrative (SG&A) expenses are high for branded pharma (31%) and biotechs (26%), due in large part to promotional costs, but lower for generics (15%). Generic companies typically do not promote their products, but do commit a higher percent of revenues to SG&A expenses related to litigation fees surrounding patent challenges. The outcome of these intellectual property battles has created much earnings uncertainty for the branded and generic companies alike.

Over the past five years, all three sectors have outperformed the S&P 500. High-growth stocks like biotechnology and generic drug stocks benefited most from the boom in 1999-2000 while branded pharmaceutical stocks were relatively flat. Since then, however, expensive biotech valuations have deflated, while the branded and generic drug sectors fared better with strong profits and healthy cash flows. Over the past year, manufacturing compliance issues, regulatory delays, and inventory management problems caused a series of unexpected earnings shortfalls in the branded pharmaceutical industry and have clouded earnings visibility, punishing sector performance.

WALL STREET'S VIEW

Revenue and earnings growth for the branded pharmaceutical industry has slowed since mid-2001, primarily due to a slew of generic entries that compete with blockbuster products. While branded pharmaceutical revenues and profits grew rapidly due to new blockbuster drugs in the mid to late 1990s, several major products lost patent protection in 2001 and 2002. "The U.S. major drug sector face[d] an unprecedented period of off-patent exposures [in 2002]," notes Kenneth Kulju of Credit Suisse First Boston. Stephen Scala of SG Cowen notes, "Following relatively light years for major patent and exclusivity expirations in 1996-99, we have seen an acceleration in new generic drug launches over the last six quarters…." The loss of revenue after generic entry for these drugs eroded profits. Carl Seiden of JPMorgan estimates that "the flurry of generics resulted in a 9-percentage point drag on industry EPS growth in 2002." The current wave of branded expirations is expected to relax in 2004 and 2005, but rise again in 2006, when "a record amount of US$17 billion in U.S. sales are at risk to experience generic competition," according to Alexandra Hauber of Bear Sterns.

The key to long-term growth is successful research and development (R&D). Investors believe that the branded pharmaceutical industry has experienced a slow-down in new product flow. Analysts are concerned by insufficient R&D productivity. Despite R&D spending increases, analysts have not observed a substantial increase in new product flow. Kulju observes, "A lack of acceleration in new molecular entity new product flow is occurring at the major pharma level despite significant increases in R&D spending…." This sentiment is echoed by David Risinger of Merrill Lynch who writes, "Despite a four-fold increase in R&D spending between 1990 and 2002, the number of NME (new molecular entity) approvals by FDA is estimated to decline from 23 in 1990 to 15 in 2002." Analysts have observed a similar decline in new products from biotechnology companies. Analysts worry that the revenue impact of the new product slow-down is exacerbated by financial losses from generic entry. Risinger believes that revenue loss from off-patent products will not be offset by revenue gain from new products until 2004.

Analysts are concerned by insufficient R&D productivity, which is further exacerbated by financial losses from generic entry.

Branded pharmaceutical companies rely upon only a handful of drugs for the majority of their revenues—the top nine U.S. manufacturers captured an average of 70% of U.S. drug sales from their top five sellers in 2001. As individual drug sales grow larger, new products must command larger markets to "move the needle." This increases pressure to develop drugs with large sales potential.

Branded pharmaceutical companies are also turning to less R&D-intensive ways of sustaining growth, *i.e.*, life cycle management. Jami Rubin of Morgan Stanley notes that "leveraging existing products is often more profitable than new product introductions, as established drugs often require less promotional spending and less time and effort than brand building." Life cycle management includes strategies such as aggressive protection of intellectual property and development of line extensions with longer patent life. For example, the manufacturer of a branded drug that is about to lose patent protection might tweak the original drug by developing a single isomer or metabolite version that has a

Drug makers are seeking to sustain growth through the extension of patents.

separate, longer patent life.[1] Recent examples include Clarinex, a single isomer form of Claritin, and Nexium, a single isomer form of Prilosec.

$30 billion of branded drugs are losing patent protection over the next four years.

The generic pharmaceutical industry has benefited from patent expirations and managed care trends that have accelerated conversion from brand to generic drugs. Scala estimates that the "more than $30B of brand drugs (2001 U.S. sales) losing patent protection over the next four years…translates to a $5-6B generic drug market opportunity." Managed care pressure has accelerated conversion from brand name to generic drugs. Kulju notes, "New pharmacy information technologies, increased managed care enrollment, higher PBM penetration, and wider generic availability have accelerated this conversion process significantly." The shift in new prescription volume from branded to generic drugs has accelerated. According to Kulju, following generic entry, it used to take six months for the volume of new prescriptions for a branded drug to fall by 50%. It now takes only six to eight weeks.

Branded and generic pharmaceutical companies have aggressively litigated intellectual property disputes. Hauber notes that over the past two years there has been a steep acceleration in generic drug challenges of existing patents. At the same time, branded pharmaceutical companies have increased the number of patents listed per compound with FDA.

The next frontier of cost containment may come from cost-benefit analysis of therapeutics.

The branded pharmaceutical industry faces increasing pricing pressure. Analysts believe branded drug pricing moderated in 2002, "largely tied to managed care pricing pressures and the influence of generic erosion," according to Kulju. Managed care buyers face increasing cost-containment pressure in difficult business environments and have been driving generic substitution and cost-containment by use of tiered co-payment plans in formularies and cost management pressures on health sponsors, according to Scala. After negotiating volume-based drug price discounts and rebates, Risinger predicts that the next frontier of cost containment will come from cost-benefit analysis of therapeutics. This has begun to influence formulary decisions in the private sector.

Despite recent earnings pressure, the branded pharmaceutical industry remains highly profitable and growth should accelerate in 2003. Despite recent generic entry and managed care pressure, the pharmaceutical industry remains highly profitable. Risinger notes, "Despite earnings disappointments, the pharmaceutical industry maintains a very healthy financial position and generates strong cash flow." Analysts agree that earnings weakness in 2002 will result in easier growth comparisons in 2003. Seiden cautions, however, "In our view, the drug industry is riskier today, with increasing separation of the winners and losers rendering assumptions that weak players today will regress upward to the mean as potentially flawed." In other words, variance in financial performance of individual drug companies may continue to increase.

Pharmaceutical investors monitor political rhetoric and regulatory oversight. The increasing political attention on the pharmaceutical industry has led many Wall Street analysts to publish regularly on legislative and regulatory issues. Investors monitor these political shifts and media attention that can affect market valuations. Investors welcome

[1] A metabolite is any substance produced or used during metabolism (digestion). In drug use, a metabolite usually refers to the end product (*i.e.*, what remains after metabolism). An isomer is a chemical species with the same number and types of atoms as another chemical species, but possesses different properties. One isomer may have a favorable clinical profile over another isomer or a mixed combination.

the installment of a permanent FDA Commissioner and the agency's reorganization plans as well as articulation of the agency's "risk-based approach" for drug approval. Compliance with FDA manufacturing guidelines has resulted in several high-profile suspensions of manufacturing plants that have had significant economic costs to manufacturers. Analysts also are aware of continuing oversight by the Department of Justice (DOJ) and Federal Trade Commission (FTC) of anti-competitive pricing and marketing practices.

Investors scrutinize Medicare coverage and payment policy because it can also influence private payors.

Although Medicare establishes payment methods for a limited number of drugs, investors scrutinize Medicare coverage and payment policy because it can also influence private payors. Investors have been closely monitoring a potential Medicare drug benefit. Kulju speculates that a "phased-in implementation" would be manageable. Scala believes a Medicare drug benefit "should be a substantial positive [for the industry], although debate surrounding the issue will be contentious." While Risinger also believes a Medicare drug benefit that is "acceptable to pharmaceutical manufacturers" is possible, he writes:

A Medicare drug benefit could result in long-term pressure on industry margins.

> [I]t is important to note that we view prospective government involvement in the drug industry as a long-term negative. When the government becomes a materially larger buyer of pharmaceuticals, it will likely become more heavy-handed with respect to drug pricing. Although additional volume may offset price concessions for drug companies when a drug benefit is initially adopted, the "price-for-volume" game is a slippery slope… and industry margins could end up under long-term pressure.

Investors tend to evaluate biotechnology companies somewhat differently from pharmaceutical counterparts. Most Wall Street investment firms have separate research analysts for the branded pharmaceutical, generic pharmaceutical, and biotechnology industries, because of the variation of each business model. Unlike the more mature pharmaceutical companies that generate strong profits, biotech companies generally incur losses for years while developing a first commercial product. Only about ten profitable biotech companies exist.

Investors question whether the pharmaceutical industry is still a "defensive" sector during uncertain economic times, due to a recent string of unexpected earnings announcements. Wall Street has historically viewed pharmaceutical stocks as "defensive," as financial performance is generally independent from the performance of the overall economy, and have been considered to provide safe, predictable growth.

One measure of a stock or sector's relative risk level is the beta coefficient.

Beta coefficients display the historical volatility of a selected stock compared to a broad based market index. The market's overall performance, represented by proxies such as the Standard & Poor's 500 Stock Index, has a beta coefficient of 1.0. A stock with a beta higher than 1.0 is more volatile than the market, and a stock with a beta lower than 1.0 can be expected to rise and fall more slowly than the market.

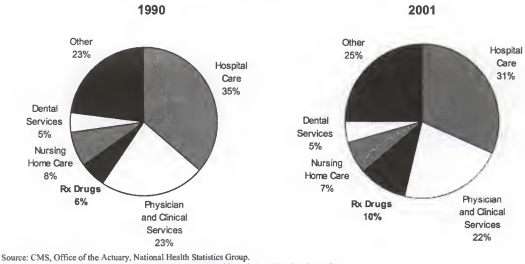
Over the past 24 months, historical beta coefficients for the drug industry have signaled less volatility than the S&P 500. The top nine U.S. branded pharmaceutical companies have an average beta of 0.74 and the top five generic pharmaceutical companies have an average beta of 0.85, indicating that these sectors are marked with relative stability. The average raw beta coefficient of the biotechnology industry is just above the S&P 500 at 1.10, meaning this sector is slightly more volatile than the market as a whole.

A recent string of unexpected announcements that earnings would be lower than originally forecast, however, has undermined the assumption that the pharmaceutical sector is defensive. Seiden writes, "The days of downside EPS risk being measured in pennies, or at worst nickels, have been lost in the seemingly mammoth disappointments over the last year…." In addition to generic pressure, other announcements related to manufacturing compliance, regulatory delays, and inventory management problems have further clouded earnings visibility. Risinger notes that as of November 2002, only one major U.S.-based pharmaceutical company had provided "clear, comprehensive [financial] assumptions for 2003."

INDUSTRY OVERVIEW

In 2001, prescription drug[2] spending in the U.S. totaled $141 billion.[3] Prescription drugs are the third largest component of national health expenditures, after hospital and physician services, and account for 10 cents of every health care dollar spent in 2001, compared to 6 cents in 1990. Although drug spending is only 10% of national healthcare spending, drug spending as a percent of total healthcare spending for working-aged adults with low hospitalization rates is 20-25%. Sicker patients typically have much higher hospital costs, and thus spend a lower relative amount on prescription drugs.

Figure 1. National Health Expenditures, 1990 and 2001



Source: CMS, Office of the Actuary, National Health Statistics Group.
Note: Prescription drug sales are reported at the retail level, and include both brand and generic drugs.

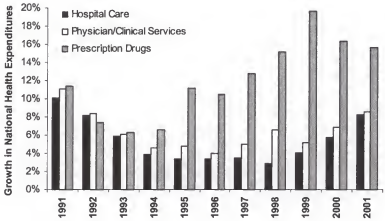
Drug spending is estimated to reach 14.2% of total national health expenditures in 2010.

CMS' Office of the Actuary projects national drug spending will reach 14.2% of total national health expenditures in 2010. Analysts attribute the rising prescription drug expenditures to a variety of reasons, including increased utilization, an aging population, development of new therapeutic agents for chronic conditions, consumer demand, and rising drug prices.

Prescription drugs are the fastest-growing segment of overall national health expenditures. From 2000 to 2001, total national health expenditures grew 8.7% from $1.31 trillion to $1.42 trillion. Prescription drug spending grew 15.7%, from $122 billion to $141 billion. In contrast, hospital care grew 8.3%, physician and clinical services grew 8.6%, and nursing home care grew 5.5%. Although drug spending has grown nearly twice as fast as all other health services since 1995, growth has moderated in recent years due to a deceleration in the rate of new product introductions and cost-containment driven by tiered formularies. The growth rates for drugs, physician and clinical services, and hospital care spending are shown in Figure 2.

[2] Throughout this discussion, the term "drugs" should be assumed to include both drugs and biologicals unless otherwise specified.
[3] CMS, Office of the Actuary, National Health Statistics Group.

Figure 2: Growth Rate of National Health Expenditure Components



Source: CMS, Office of the Actuary, National Health Statistics Group.

Hospital spending remains the largest dollar component of health expenditure growth.

While drug spending has been the fastest growing component of national health expenditures, the increase in hospital care spending was the largest dollar component of national health expenditure growth. In 2001, hospital spending grew 8% to $451 billion while prescription drug spending grew 16% to $141 billion.

The top ten pharmaceutical companies account for 60% of U.S. drug sales. The industry remains relatively fragmented, with the top company owning only a 10% share of the U.S. pharmaceutical market in 2001. The top 10 companies by U.S. drug sales are large, research-based, branded pharmaceutical companies. No generic drug manufacturers are included in the top ten by sales. In fact, 2001 generic drugs accounted for 47% of dispensed prescriptions, but only 8% of dollar sales.

A brief examination of companies ranked by U.S. prescription drug sales demonstrates the global nature of the pharmaceutical business. Two of the top ten drug makers are domiciled overseas. Indeed, most major pharmaceutical companies also have extensive sales and operations in foreign markets. After North America, Europe and Japan are the largest regional markets in terms of prescription drug dollar sales. Also, international manufacturing operations in countries such as Puerto Rico and Ireland can benefit the tax structure of a global pharmaceutical company.

Figure 3: Top 10 Pharmaceutical Manufacturers by U.S. Prescription Sales, 2001

Company	U.S. Sales	Market Share
Pfizer	$17,631	10.0%
GlaxoSmithKline	15,474	8.8%
Merck	12,519	7.1%
Johnson & Johnson	10,922	6.2%
Bristol-Myers Squibb	10,505	6.0%
AstraZeneca	10,067	5.7%
Lilly	7,627	4.3%
Wyeth (formerly American Home Products)	6,983	4.0%
Novartis	6,787	3.9%
Pharmacia	6,512	3.7%
Top 10 Companies	**$105,027**	**59.7%**

Source: IMS Health, Retail and Provider Perspective 2002.
Note: Represents prescription pharmaceutical purchases including insulin, in millions, at pharmacy acquisition costs by retail food stores and chains, mass merchandisers, independent pharmacies, mail services, non-federal and federal hospitals, clinics, closed-wall HMOs, long-term care pharmacies, home health care, and prisons/universities.

Successful research and development is the key driver for long-term growth. As the branded pharmaceutical industry's products face continued competition from generic products, revenue growth must be spurred by successful research and development efforts to develop new products. Stephen Scala of SG Cowen points to a "parallel between development and market size [that] makes sense given that pharmaceutical companies attempt to develop and market large potential drugs in an effort to sustain sales and EPS growth." As one product successfully grows a company's revenue base, subsequent product launches must command even larger markets in order to have an impact of overall revenue growth.

R&D spending, critical for developing robust pipelines, may be reined-in during profit crunches. The long-term profit impact of changes to R&D spending is uncertain. The Office of Technology Assessment found in 1993 that "lags of ten to fifteen years from peak R&D spending to peak profitability for new products are typical." It is difficult, however, to show a direct correlation between R&D spending and the number of new drug launches. Steve Scala points out the difficulty of assessing pipelines based solely on the number of candidates, "More pipeline targets may result in more promising drugs being brought to market, or more pipeline targets may mean more pruning is necessary before promising drugs are uncovered...."

Branded pharmaceutical companies rely on a few large, blockbuster products for a majority of their revenue.

Both branded and generic pharmaceutical companies fiercely litigate intellectual property. As the major branded pharmaceutical companies have worldwide sales bases typically over $10 billion, the importance of blockbuster products (generally considered products with more than $500 million in annual sales) has risen. The top five drug families averaged 70% of U.S. drug sales for each of the top nine U.S. branded drug companies in 2001, as shown in Figure 4. Conversely, when a branded blockbuster product experiences competitive generic entry, financial performance can be significantly impacted. As individual drug sales increase and the stakes rise, both the branded pharmaceutical companies and the generic drug manufacturers have grown increasingly aggressive about litigating intellectual property. The number of generic drug applicants seeking market entry prior to patent expirations has been increasing, as well as the number of patents listed by brand manufacturers at the FDA. A typical first generic entrant will take roughly one-half of new prescription volume within six to eight weeks. Any change in timing of generic entry can have a substantial revenue impact on both the branded and generic pharmaceutical companies.

Figure 4: Top 5 Drug Families for Major U.S. Branded Drug Companies

($ in millions)

Company	Top 5 Drugs (by U.S. Sales)	2001 U.S. Sales	% of Total U.S. Rx Sales
Abbott	Depakote franchise	$869	23%
	Biaxin	$537	14%
	Synthroid	$445	12%
	Flomax	$411	11%
	Tricor	$264	7%
	Top 5 Abbott	*$2,526*	*67%*
Bristol Myers-Squibb	Glucophage franchise	$2,655	24%
	Pravachol	$1,366	12%
	Plavix	$1,189	11%
	Paraplatin	$583	5%
	Taxol	$545	5%
	Top 5 Bristol Myers-Squibb	*$6,338*	*56%*
Johnson & Johnson	Procrit	$2,335	23%
	Risperdal	$1,240	12%
	Floxin/Levaquin	$993	10%
	Oral contraceptives	$892	9%
	Remicade	$687	7%
	Top 5 Johnson & Johnson	*$6,147*	*60%*
Lilly	Zyprexa	$2,176	31%
	Prozac	$1,659	24%
	Humulin	$579	8%
	Evista	$526	7%
	Gemzar	$417	6%
	Top 5 Lilly	*$5,357*	*76%*
Merck	Zocor	$4,690	39%
	Vioxx	$1,895	16%
	Fosamax	$1,275	10%
	Prinivil/Prinizide	$1,165	10%
	Singulair	$1,060	9%
	Top 5 Merck	*$10,085*	*83%*
Pfizer	Lipitor	$4,423	29%
	Zoloft	$1,929	13%
	Neurontin	$1,510	10%
	Norvasc	$1,667	11%
	Zithromax	$1,137	7%
	Top 5 Pfizer	*$10,666*	*70%*
Pharmacia	Celebrex	$2,447	35%
	Ambien	$896	13%
	Camptosar	$566	8%
	Detrol	$488	7%
	Xalatan	$391	6%
	Top 5 Pharmacia	*$4,788*	*68%*
Schering-Plough	Claritin franchise	$2,716	54%
	Intron A franchise	$750	15%
	Nasonex	$391	8%
	Proventil	$230	5%
	Kdur	$213	4%
	Top 5 Schering-Plough	*$4,300*	*85%*
Wyeth	Premarin family	$1,796	27%
	Effexor	$1,098	17%
	Prevnar	$767	12%
	Protonix	$561	8%
	Cordarone	$265	4%
	Top 5 Wyeth	*$4,487*	*67%*
AVERAGE	**Top 5 Drugs**	**$6,077**	**70%**

Source: Company reports.

R&D-Based Industry

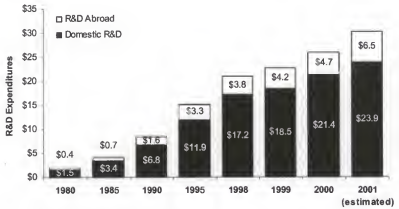
The branded pharmaceutical and biotechnology industries depend on innovative R&D to produce new medical treatments that are the key drivers for long-term growth, making R&D the most important expense item for the industry. As the branded pharmaceutical industry's products face continual generic exposure, revenue growth demands new product launches. According to a 1999 Office of Technology Policy report, nine of the top twenty U.S. corporations ranked by R&D spending were pharmaceutical companies in 1997.

Rising Costs

According to the industry, estimated pharmaceutical R&D spending totaled $30.3 billion in 2001, a 16.6% increase over 2000.[4] Annual R&D growth has rapidly accelerated in recent years, up from 8% in 1999, 15% in 2000, and 17% in 2001, as can be seen in Figure 5 below. R&D expenditures include salaries of researchers, cost of materials used in research, and related overhead costs. Although other expenses also may be classified as R&D, public filings for the large diversified pharmaceutical companies usually do not separate pharmaceutical-related R&D expenses from other operations.

Figure 5: Pharmaceutical R&D Spending

($ in billions)



Source: PhRMA Annual Membership Survey, 2002.

R&D expenses have risen dramatically over the past decade, for a variety of reasons according to Wall Street analysts and industry sources. Although there is no consensus explanation, several typical arguments are:

1. In the mid-1990s, industry took the view that managed care would reimburse only true breakthrough innovations. The industry took bigger R&D risks in an effort to hit more home runs, but ended up striking out a lot.
2. R&D focus has shifted to develop drugs for chronic or more complex diseases with large market potential. These chronic conditions, however, often involve much larger patient populations that require more expensive trials.
3. Commercial markets for certain existing drug classes have become saturated, decreasing the profit opportunities to be gained by developing variations in the

[4] R&D spending by U.S.-owned pharmaceutical firms with membership in Pharmaceutical Research and Manufacturers of America (PhRMA) trade organization. Spending estimates include domestic and oversees R&D.

same drug class. Pharmaceutical companies therefore turn to more innovative and riskier scientific research to create new markets. This type of research increases R&D investment cost.

Because variable R&D expenses are relatively easy to control during periods of earnings pressure, analysts often view high R&D spending levels as a healthy sign of sustained ongoing commitment to long-term growth. There is no definitive data, however, to either prove or disprove the correlation between overall R&D spending and pipeline productivity. A 1993 Congressional study noted that "lags of ten to fifteen years from peak R&D spending to peak profitability for new products are typical."[5]

Tax credits are a significant benefit to the drug industry.

The pharmaceutical industry enjoys certain tax benefits for the costs of R&D. A pharmaceutical company can expense R&D costs (reducing taxable income in a given year) rather than depreciate them over time. A pharmaceutical company also receives tax credits that depend on domestic spending levels for certain categories of R&D. Tax credits are a significant benefit to the sector, but the amount a specific pharmaceutical company benefits from these tax credits depends on its particular financial structure.

Role of FDA

Like CMS, the Food and Drug Administration (FDA) is a federal agency within the Department of Health and Human Services.[6] The primary responsibility of FDA is protecting public health by permitting safe and effective products to reach the market in a timely manner and monitoring products for continued safety after they are in use. FDA grants or denies approval of all applications for new drugs and biologicals, and thus acts as the gatekeeper for new pharmaceutical products. FDA can also withdraw pharmaceuticals from the marketplace if post-marketing surveillance suggests public health risks outweigh benefits.

FDA Approval Timelines

In fiscal 2002, PDUFA required FDA to act on 90% of new drug applications with in 10 months.

Timelines between acceptance of a new drug application (NDA) and approval have shortened significantly under the Prescription Drug User Fee Act (PDUFA), enacted in 1992 and renewed in 1997 and 2002. Under PDUFA, FDA collects user fees from the companies that submit new drug applications (NDAs) and biologics license applications (BLAs). In exchange for these fees, companies are given assurance that FDA will examine applications according to an expeditious timeline. In fiscal 2002, PDUFA required FDA to act on 90% of new drug applications within 10 months. In 2001, median total approval time for priority applications was 6 months, less than half of what it was in the early PDUFA years. Median approval time for standard applications was 12.5 months for fiscal 2000 submissions, a slight increase from 12.0 months for 1999 submissions.

In FDA's 2001 PDUFA Performance Report, FDA notes that the number of new product applications filed each year under PDUFA increased from 1993 to 1997, leveled off until 2000, and then dropped substantially in 2001. New drug applications dropped 25% in 2001. The decline was even more pronounced by the decline of priority applications (that generally represent the most significant therapeutic gains), which were down 60% in 2001.

[5] U.S. Congress, Office of Technology Assessment. *Pharmaceutical R&D: Costs, Risks, and Rewards*, February 1993.
[6] For information on the role of CMS in determining coverage and payment, please see pages 42-47.

PDUFA encourages FDA to take steps to speed drug development not only during application filing, but also over all stages of the drug development process. Most drug sponsors seek an active dialogue throughout the entire drug development process, but particularly before Phase III and NDA or BLA application filing to ensure that the sponsor and FDA have some tentative agreement as to the requirements. In 2001, FDA received 1,471 requests for formal meetings from sponsors (an increase of 24% over 2000) and scheduled 1,361 meetings (an increase of 21% over 2000). Under PDUFA 2002, FDA must provide "information request" letters to notify sponsors of deficiencies in applications within 14 days of filing, for at least 50% of applications in 2003 and rising to 90% by 2005.

FDA Approval Process

Average drug development takes 8.5 years.

The length of time between early laboratory and animal testing to FDA approval for a new drug varies greatly, with FDA estimating that the average development timeline is 8.5 years. The various steps required for FDA approval are described below.

After laboratory and animal testing of a new compound, the innovator files an investigational new drug (IND) application to test the compound in clinical (*i.e.*, human) trials. FDA either approves or rejects the IND, or allows a 30-day grace period to pass without objection.

Clinical testing is broken down into three "phases." Phase I studies are the initial human trials, usually conducted in healthy volunteers. These initial trials test compounds for safety, tolerance, and pharmacokinetics (*i.e.*, absorption, distribution, metabolism, and excretion of drugs). Phase II studies generally test the compound in patients with the condition the drug is intended to treat. Dose and dosing regimen are explored, often to establish an upper and lower bound. Phase III trials are the critical trials that seek the most complete safety and efficacy data in the target conditions. To consider a new drug for approval, FDA generally requires two randomized, well-controlled trials with proof of safety and efficacy, and these are usually Phase III trials.

Upon completing clinical trials, a drug sponsor submits a new drug application (NDA) to FDA's Center for Drug Evaluation and Research (CDER) for review. A new biologic requires the submission of a Biologic License Application (BLA) to FDA's Center for Biologics Evaluation and Research (CBER). The conventional difference governing the type of application to be filed is whether the therapeutic is manufactured by a chemical process (and is classified as a drug) or a biological process (and is classified as a biologic). FDA has recently announced an agency reorganization in which CDER will review both NDAs and therapeutic BLAs, given that these products have similar clinical development issues, data analysis, and clinical uses. CBER review will focus on vaccines, blood products, tissue products, and gene therapy.

Break-through therapeutics may be granted six-month priority review by the FDA.

Most drugs are reviewed under the standard 10-month PDUFA timeline. Drug sponsors may submit applications for priority review (fast-track), which is granted at the FDA's discretion. Priority review is only 6 months, and is reserved for therapeutics that promise a significant clinical break-though for serious or life-threatening conditions for which no other therapeutic alternatives exist. Priority review drugs may be approved on surrogate endpoint data and the commitment of the drug sponsor to continue carrying out post-marketing studies to confirm its safety and efficacy.[7]

Occasionally, FDA will request a recommendation on an application from an advisory committee. FDA employs 18 advisory committees, comprised of experts around a central medical area, which advise on issues including approval or warning information on side effects.

The PDUFA deadline can be met by an approval letter, an approvable letter, or a not-approvable letter. Whereas approval and rejection are relatively straightforward, an "approvable" letter is an approval contingent upon satisfactory answers to final FDA questions. These questions are typically about narrow or minor parts of the application, or concern final wording of a drug's product monograph or label. In these cases, a final approval usually follows within a few months. Approvable letters seem to have become more common as a response of some kind must be delivered by the PDUFA deadlines.

After the drug is launched, a sponsor may conduct Phase IV studies to study adverse effects or long-term safety. Phase IV studies can also address new indications and expanded populations or provide head-to-head comparison data versus competitors.

Patent and Exclusivity Protection

Patents are generally valid for twenty years from the date of filing. Although most pharmaceutical patents are filed during pre-clinical testing, additional patents can be filed at any time given that drug development is an ongoing process. Thus, the effective patent life of a compound once it is commercialized is less than twenty years. There are four types of pharmaceutical patents: composition of matter, method of use, formulation, and manufacturing. In general, the two strongest types of patents for a compound are composition of matter and primary method of use.

Besides patent life, there are several other important pharmaceutical exclusivity protections defined by statute. For any single drug, branded drug manufacturers will often have several patents or other forms of market exclusivity protection. Patents will likely have staggered expiration dates and may not all stand the same level of scrutiny from generic challengers. These provisions are summarized in Figure 6 below.

[7] A surrogate endpoint of a clinical trial is a laboratory measurement or a physical sign used as a substitute for a clinical endpoint. Changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinical endpoint. A clinical endpoint directly measures how a patient feels, functions, or survives. An example of a surrogate endpoint is tumor shrinkage from cancer treatment, whereas a clinical endpoint might include mortality benefit from that treatment.

Figure 6: Summary of Pharmaceutical Patent and Other Exclusivities

Protection	Description	Duration
Patent	Types of pharmaceutical patents include: composition of matter, method of use, formulation, product by process.	20 years from date of filing
5-year Hatch-Waxman Exclusivity	Granted to new chemical entities (NCE). If no unexpired patents are listed with FDA, generics can file after this exclusivity expires. If unexpired patent(s) are listed, generics can file one year before this exclusivity expires but cannot be approved until after expiration.	5 years from date of approval
3-year Hatch-Waxman Exclusivity	Granted to modified versions of existing drugs with new clinical data (*e.g.*, new dosage form, new clinical use). This exclusivity applies to only the modification of the drug product. Generics can file at any time but cannot be approved until after expiration.	3 years from date of approval
Orphan Drug Exclusivity	Granted to drugs for indications with less than 200,000 U.S. patients. Protects against approval of both generic and other branded versions of same drug for same indication.	7 years from date of approval
Pediatric extension	Granted in exchange for pediatric studies for a drug as requested by FDA.	6 months added to protecting exclusivity or patent life
"First-to-file" exclusivity for generics	Generic exclusivity granted to the earliest generic applicant prior to expiration of listed patents for brand version. No other generic versions can be approved during exclusivity.	180 days from date of commercial launch or court decision declaring patents invalid or not infringed

Sources: CMS and FDA.

Many of these exclusivity provisions were created by the Drug Price Competition and Patent Term Restoration Act of 1984, otherwise known as the Hatch-Waxman Act, the single most important piece of legislation to affect the modern pharmaceutical industry. To encourage companies to develop compounds for commercialization in the U.S. on which the primary composition of matter patent had already expired, Hatch-Waxman created provisions for five-year exclusivity for active compounds that have never been approved in the U.S., called new chemical entities (NCEs). Five-year exclusivity is granted if the NCE has no patents listed in the Orange Book, an FDA-maintained register of all patents related to a specific new drug application. Drug applications that rely on clinical data for an NCE, including generic drug applications called abbreviated new drug applications (ANDA), will not be accepted by FDA until the five years have expired. Generics cannot launch until their ANDAs receive final approval, which typically takes another 12 to 18 months. Five-year exclusivity may also be granted to compounds that may have one or more patents listed in the Orange Book. In these cases, an ANDA can be filed one year prior to the five-year expiration if also accompanied by paragraph IV certification[8] against at least one unexpired patent.

To encourage improvement of and new indications for older medicines that are already approved, Hatch-Waxman also created provisions for three-year exclusivity. A generic application may be filed at any time during these three years, but the generic cannot be approved until expiration of all exclusivities and patent life. This exclusivity generally applies to a variety of product changes or improvements to existing products on the market, such as changes in dosage form, product strength, substitution of the active ingredient for a combination product, formulation, dosage regimen, or a metabolite/isomer form.[9]

If a drug sponsor responds to an FDA request for additional pediatric clinical studies, FDA may grant an additional six months of exclusivity.

[8] For explanation of paragraph IV certification, please see pages 17-18.

[9] A metabolite is any substance produced or used during metabolism (digestion). In drug use, a metabolite usually refers to the end product (*i.e.*, what remains after metabolism). An isomer is a chemical species with the same number and types of atoms as another chemical species, but possesses different properties. One isomer may have a favorable clinical profile over another isomer or a mixed combination.

Patient populations under 200,000 are generally considered too small to assume the costly and risky pursuit of a new therapeutic. The National Organization for Rare Disorders estimates that there are 6,000 rare diseases that afflict 25 million Americans. To encourage companies to develop new therapeutics for commercially less attractive markets, Congress passed the Orphan Drug Act of 1983. Orphan drugs are drugs developed for diseases that are projected to affect fewer than 200,000 Americans. Orphan drug exclusivity prohibits an identical competing product for seven years after gaining approval, in addition to special tax credits for clinical research.

Generic Drugs

Abbreviated New Drug Application Process

Arguably, the most important result of the Hatch-Waxman Act was the creation of the abbreviated new drug application (ANDA) process. The ANDA process streamlined approval requirements for a generic drug through the bioequivalence standard. The standard of bioequivalence demands the generic drug must deliver the same amount of active ingredient in the same timeframe as the brand product. The creation of ANDA increased generics' access to the marketplace.[10] Generic adoption was supported by the passage of substitution laws at the state level throughout the 1980s, which allowed pharmacists to fill brand name prescriptions with generic versions unless specifically specified. Generic prescriptions as a percent of total prescriptions, according to IMS, have risen from 19% in 1984 to 47% in 2001.

Generic adoption was supported by the passage of substitution laws, which allowed pharmacists to fill brand name prescriptions with generic versions.

Each ANDA must be filed with one of four certifications as outlined in statute. Each certification refers to the brand drug's patents as listed on the Orange Book, an FDA-maintained register.

- Paragraph I – The brand drug is not patented.
- Paragraph II – All patents have expired.
- Paragraph III – The generic will not be marketed until all patents expire.
- Paragraph IV – All patents are not infringed or are invalid.

Paragraph IV Filings and the 30-Month Clock

Predictably most patent litigation between brand and generic pharmaceutical companies center around "paragraph IV" filings. Such filings require the generic pharmaceutical manufacturer to notify the NDA holder of the pending patent challenge, and the NDA holder has 45 days from date of notification to initiate litigation against the generic company. The initiation of litigation triggers a 30-month clock, during which the generic drug cannot be approved until the earliest of 1) the date the patents expire, 2) determination of non-infringement or invalidity by a court during patent litigation, or 3) the expiration of the 30-month clock.

Under current law, multiple 30-month stays may significantly delay generic entry.

If a new patent is filed on the Orange Book after a generic company has filed an ANDA, an additional 30-month stay may be generated. In this situation, the generic applicant must certify that either its product does not infringe the new patent or the new patent is invalid. The brand-name company can again sue within 45 days of this new notification, which triggers a new 30-month clock.

[10] Until 1962, drugs were approved for safety only. Although never approved in the U.S., the tragedy of thalidomide, a morning sickness treatment that caused severe birth defects internationally, resulted in the 1962 drug amendments to the Federal Food, Drug, and Cosmetic Act, which added an efficacy requirement for new drug approvals. The amendments also changed the process for getting a generic drug on the market, but were largely unsuccessful due to the extensive filing requirements for the generic filer.

To incent paragraph IV challenges to existing patents, Hatch-Waxman also provided for six months of exclusivity for the first generic to file an ANDA and successfully win a court challenge over a branded drug. During this time, no other generic can be given full approval. Much of the economic value of a generic drug's life cycle is captured during this six-month exclusivity period—increasing generic manufacturers incentive to file earlier challenges to brand name patents.

Generic drug makers have become much more aggressive about filing for generic drug approval prior to patent expiration. Paragraph IV filings, as a percent of all ANDAs, have increased significantly, accounting for only 2% in the 1980s, 12% in the 1990s, and from 1998-2000, approximately 20%, according to FTC analysis. According to Bear Sterns, although there were only 24 paragraph IV filings in the first eight years after the enactment of Hatch-Waxman, there were 104 filings in the next eight years. In the past 20 months, there have been 50 paragraph IV filings. At the same time, brand manufacturers have increased the number of patents listed per compound in the Orange Book.

An FTC study of generic drug entry found that on average, the time required for FDA review and approval was 25 months and 15 days for paragraph IV ANDA filings where the generic company was not sued. In cases where the applicant was sued, the average time between patent filing and district court decision was 25 months and 13 days, and the average time between a patent infringement suit and court of appeals decision was 37 months and 20 days.

Because the final court of appeals decisions typically takes 7 months more than the 30-month clock, investors are often more concerned about tracking litigation rather than expiration of patent or exclusivity terms. Joe Riccardo at Bear Sterns notes, "In many cases, tracking patent infringement litigation and other requirements for [generic] approval… has become much more important than just tracking patent expiration dates." It is rare for a generic manufacturer to launch a generic drug before a final appellate decision. The generic company would be responsible for treble damages if it were found to have infringed valid patents.

Litigation of future paragraph IV filings may take even longer, since the FTC analysis suggests that cases involving multiple patents take longer than those with fewer patents. FTC reports, "As of June 1, 2002, for 6 out of the 7 cases that have been pending for more than 30 months before a district court, the brand-name company has alleged infringement of 3 or more patents." This compares to pre-1998, when only one out of nine blockbuster drug products had 3 or more patents challenged. FDA has no ability to dictate which patents are listed on the Orange Book, and does not have administrative procedures for resolving listing disputes. A party may challenge the accuracy of a newly listed patent, and FDA will seek to confirm this patent with the patent holder, but will not withdraw the patent unless the patent holder agrees voluntarily. This has been upheld in two district courts to date.

FDA Proposed Changes to Hatch-Waxman

On October 24, 2002, FDA published a proposed rule that would make three major changes to current application of the Hatch-Waxman Act.

- First, brand name companies would be allowed only one 30-month stay when a generic company challenges a brand drug's patents, ending multiple 30-month stays that can be triggered by the listing of a new patent for the brand drug. This is similar to an FTC recommendation and Senate bill proposal.
- Second, Orange Book patent listings would exclude patents claiming metabolites, packaging, and intermediates.
- Third, brand name companies would be required to list more detailed information when filing a patent and to certify that the information is true.

The proposed rule was published in the Federal Register and public comments were solicited over the following 60 days.

These elements of the FDA proposal are also incorporated into a leading Senate bill. This proposed bill also establishes a private right of action (in which a generic company can sue a brand name drug company if it believes a frivolous patent has been filed), limiting 30 month stays to patents filed within 30 days of the approval of the original NDA, allowing a brand name company to sue a generic paragraph IV filer within 45 days or give up the right to sue over that application.

INDUSTRY PERFORMANCE

U.S. pharmaceutical companies are highly profitable.

The nine major U.S. branded pharmaceutical companies include Abbott, Bristol Myers-Squibb, Johnson & Johnson, Eli Lilly, Merck, Pfizer, Pharmacia, Schering Plough, and Wyeth. The major U.S. pharmaceutical companies are highly profitable. In addition to pharmaceuticals, the major companies all have diversified revenue streams that typically include medical devices and supplies, veterinary products, and consumer products. Because pharmaceutical companies typically do not provide detailed information about the operating performance of the pharmaceutical business alone, the following analysis relies on the available data for the overall company, unless specified otherwise.

Most biotech companies are unprofitable.

This analysis also provides similar data for the biotechnology and generic drug industries, given their importance in the prescription drug market. Most biotechnology companies are still developing first products for commercialization. Because most biotech companies are unprofitable, this industry analysis represents only a subset of companies that have achieved consistent profitability over the past few years, and is not representative of the biotech sector as a whole. This subset of biotech companies includes Amgen, Biogen, Cephalon, Chiron, Genentech, Genzyme, Idec, Immunex (prior to acquisition by Amgen in 2002), and MedImmune. For the generic drug industry, the five generic drug companies that sold the highest volume of generic prescriptions in 2001 are included. They are Andrx, Barr, Ivax, Mylan, and Watson.

Figure 7: Market Cap of Selected Pharmaceutical and Biotechnology Companies

($ in millions)

Company	Ticker	Market Cap	Company	Ticker	Market Cap
U.S. Branded Pharmaceuticals			**Biotechnology**		
Abbott Laborstories	ABT	$ 63,189	Amgen Inc	AMGN	$ 63,311
Bristol-Myers Squibb Co	BMY	47,942	Biogen Inc	BGEN	6,171
Johnson & Johnson	JNJ	168,759	Cephalon Inc	CEPH	2,737
Eli Lilly & Co	LLY	75,255	Chiron Corp	CHIR	7,382
Merck & Co, Inc	MRK	132,465	Genentech Inc	DNA	17,659
Pfizer Inc.	PFE	195,834	Genzyme Corp	GENZ	6,512
Pharmacia Corp	PHA	56,268	Idec Pharmaceuticals Corp	IDPH	5,156
Schering-Plough Corp	SGP	33,908	Medimmune Inc	MEDI	7,079
Wyeth	WYE	51,442			
Top 9 U.S. Branded Pharma		$ 825,061	**Top 8 Biotech**		$ 116,006
Generic Pharmaceuticals					
Andrx Corp	ADRX	$ 1,056			
Barr Laboratories Inc	BRL	2,974			
Ivax Corp	IVX	2,364			
Mylan Laboratories	MYL	4,500			
Watson Pharmaceuticals Inc	WPI	3,123			
Top 5 Generic Pharma		$ 14,017			

Sources: Bloomberg and company reports. As of January 3, 2002.
Note: Market capitalization is one measure of a company's value or size, calculated by multiplying share price by the number of shares outstanding. Wall Street analysts may categorize certain companies under varying sectors (*e.g.*, Abbott and Johnson & Johnson are often covered by medical technology analysts).

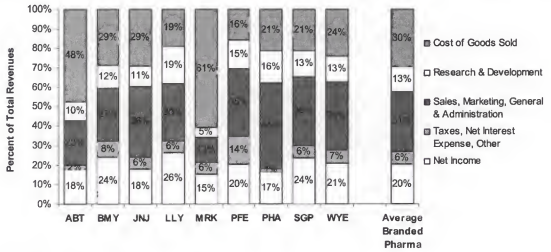
[11] While payors provide some overall discretion or design parameters, formulary decisions are usually made by a PBM's pharmacy & therapeutics (P&T) committee which is comprised of independent physicians and pharmacists who review the clinical effectiveness of each drug, and then evaluate them based on publicly available pricing information. PBMs then negotiate with manufacturers for rebates and discounts.
[12] In 1993, Merck, SmithKline Beecham and Eli Lilly each acquired a PBM, but SmithKline and Lilly divested their PBMs in the late 1990s, and Merck intends to do the same.

Profits

Net income is the revenue that remains after accounting for all operating expenses and non-operating expenses (such as interest, taxes, depreciation, and amortization). This is the total profit or "bottom line." It is the amount that the business can reinvest in itself and, in the case of a for-profit company, may distribute to shareholders. Net income margin is expressed as a percent of revenue.

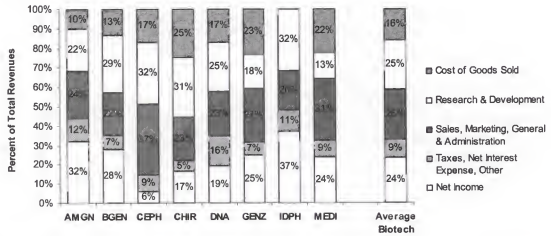
Figures 8, 9, and 10 show a side-by-side comparison of branded, biotech, and generic drug company expenses, as a percent of total revenue, as well as average net income margins for 2001. While variation from company to company exists, the differences in business models are apparent in the average expense structures of the three sectors as shown in Figure 11.

Figure 8: Comparison of Expenses and Net Income, Branded Pharma Companies, 2001



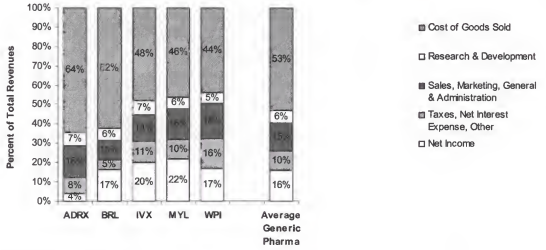
Sources: Bloomberg and analyst models.
Note: All figures exclude one-time charges.

Figure 9: Comparison of Expenses and Net Income, Biotech Companies, 2001



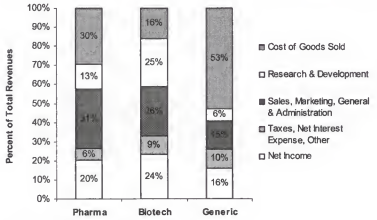
Sources: Bloomberg and analyst models.
Note: Because most biotech companies are unprofitable, these industry averages are not representative of the biotech sector as a whole but only a subset of companies that have achieved consistent profitability over the past few years. Figure excludes Immunex (acquired by Amgen in 2002).

Figure 10: Comparison of Expenses and Net Income, Generic Pharma Companies, 2001



Sources: Bloomberg and analyst models.

Figure 11: Comparison of Expenses and Net Income, Industry Averages, 2001

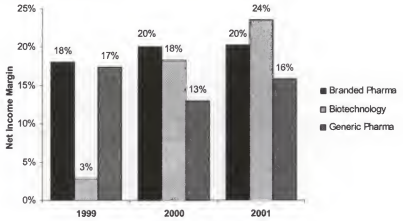


Sources: Bloomberg and analyst models.

R&D expenses as a percent of revenues are highest for the biotechs (average 25%), less for branded pharma (13%) and much less for generics (6%). SG&A spending is highest for branded pharma (31%) and comparable for biotechs (26%) due to heavy product promotion. Although generic companies traditionally do not promote their products, SG&A expenses (average 15%) are related to higher litigation fees relative to revenues.

In 2001, the biotech and branded pharma companies had average profit margins of 24% and 20% respectively, compared to the generics at 16%, largely due to differences at the gross margin level. Figure 12 shows the yearly net income for the three sectors. Given that the selection of the biotechnology companies for analysis were based on profitability, it is perhaps unsurprising to see the average biotech index profit margin improve from 3% in 1999 to 24% in 2001. Despite this selection bias, there were fewer than a dozen profitable biotech companies even in 2002. Maturing biotech companies that have reached profitability and fund their own marketing efforts more closely resemble branded pharmaceutical companies.

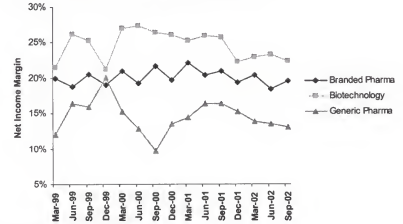
Figure 12: Average Profit Margins, Annual



Sources: Bloomberg and analyst models.
Note: Biotech average excludes Immunex (acquired by Amgen in 2002).
Note: For all charts, branded pharmaceutical companies include Abbott, Bristol Myers-Squibb, Johnson & Johnson, Eli Lilly, Merck, Pfizer, Pharmacia, Schering Plough, and Wyeth. Biotechnology companies include Amgen, Biogen, Cephalon, Chiron, Genentech, Genzyme, Idec, Immunex (prior to acquisition by Amgen in 2002), and MedImmune. Generic pharmaceutical companies include Andrx, Barr, Ivax, Mylan, and Watson. Data exclude one-time charges.

On a quarterly basis, branded pharmaceutical companies have averaged a relatively steady 20% average profit margin since 1999, while biotech companies have averaged a slightly higher 25%. Generic pharmaceutical profit margins have been more unpredictable, and highly dependent on timing of generic launches, but have averaged 15%. Because some generic launches earn 180 days of exclusivity, during which time no other generic can be launched, earnings grow rapidly in a short period of time, which skews the averages.

Figure 13: Average Profit Margins, Quarterly



Sources: Bloomberg and analyst models.
Note: Biotech average excludes Immunex (acquired by Amgen in 2002).

Revenues

The annual revenue growth of the branded pharmaceutical companies has averaged 11% per year over the past fifteen years. Quarterly revenue growth, however, has been declining since mid-2001. Industry revenue growth has been impacted by the patent expirations of several major blockbusters, which have made revenue comparisons to previous years very difficult. Carl Seiden of JPMorgan notes the company-specific reasons that have led to overall industry growth deceleration, which are shown in Figure 14:

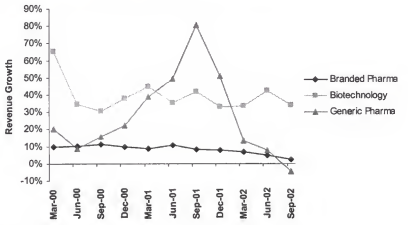
Figure 14: Company-Specific Reasons for Revenue Deceleration

Company Name	Reason(s) for Revenue Deceleration
Merck & Co, Inc (MRK)	Vasotec, Prinivil, and Pepcid generics
Bristol-Myers Squibb Co. (BMY)	Taxol, Buspar, Megace and Glucophage generics Inventory de-stocking
Eli Lilly & Co. (LLY)	Prozac generics
Pharmacia Corp. (PHA)	Return of Ambien to Sanofi
Schering-Plough Corp. (SGP)	De-stocking of Claritin Manufacturing problems on product supplies

Source: JPMorgan.

In addition to new drug launches, companies can expand revenues by increasing utilization (the number of prescriptions dispensed), changing product mix, and raising the price of existing drugs. According to Sonderegger Research Center analysis, for the period between 1997-2000, utilization contributed to 48% of the increase in prescription drug expenditures, types of prescriptions uses (shift from older, lower cost drugs to newer higher cost drugs), contributed to 28% of the increase, and price contributed to 24% of the increase. Kenneth Kulju of Credit Suisse First Boston suggests that rising drug prices have moderated in 2002, "largely tied to managed care pricing pressures and the influence of generic erosion."

Figure 15: Average Revenue Growth, Quarterly



Sources: Bloomberg and analyst models.

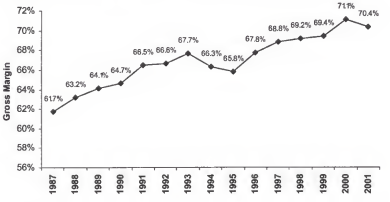
The chart above illustrates the relatively higher growth rates that generic and biotech companies have enjoyed since 2000. Generic industry revenue growth is partially the opposite trend of revenue declines for the branded pharmaceutical industry due to generic launches of blockbuster products like Prozac. Stephen Scala of SG Cowen notes, "Following relatively light years for major patent and exclusivity expirations in 1996-99, we have seen an acceleration in new generic drug launches over the last six quarters which is expected to continue over the next 3-4 years." Biotechnology companies often enjoy much higher growth rates since the impact of one or two successful products early in their life cycles can have a larger impact on a smaller revenue base.

Cost of Goods Sold

Cost of goods sold (COGS) is a manufacturer's cost of buying materials and producing finished goods. The gross margin is the percent of total revenues remaining after deducting COGS. The branded pharmaceutical companies have been improving gross margins over the past fifteen years, increasing from 62% in 1987 to 70% in 2001. Gross margin improvement may be due to factors such as increasing manufacturing efficiency, shifting product mix towards higher-margin items, and rising prices.

Figure 16: Gross Margins for Branded Pharma, Annual

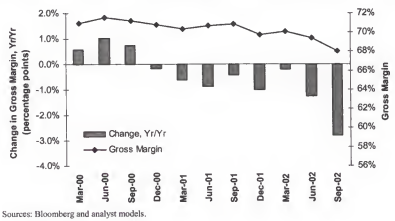
Gross margins have been improving over the last decade.



Source: Bloomberg.

This long-term trend of improving gross margins, however, has reversed in recent quarters. This has been caused, in part, by the patent expirations of several highly profitable blockbuster drugs. For a diversified pharmaceutical company, profit margins are typically highest on the prescription drugs, and lower for business lines such as consumer products or pharmacy-benefit management. When these lower-margin businesses become a higher percent of total revenues, overall gross margins decrease. This deterioration in gross margins for the pharmaceutical companies is illustrated below. The bars represent the changes in gross margins; these changes have all been negative since the third quarter of 2000.

Figure 17: Gross Margin Changes for Branded Pharma, Quarterly

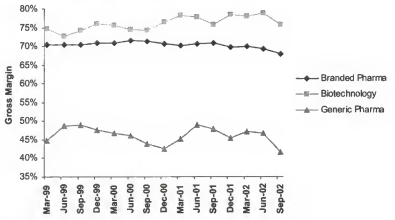


Sources: Bloomberg and analyst models.

The typical effect of a generic launch has been amplified, as generic drugs are being adopted more quickly than ever. Because 50% generic erosion now occurs six to eight weeks (rather than six months historically) after generic entry, Kulju writes, "This loss of the off-patent profit 'tail' on branded drugs creates considerable earnings management difficulties, particularly at the gross margin level."

The pharmaceutical and biotech industries have much higher gross margins than does the generic industry. Generic drugs have little competitive differentiation except for price and therefore the only way to gain share is to offer relative discounts to the brand or other generic versions. Multiple generics will increase relative discounts to the brand drug, causing rapid price erosion of a market. Biotechnology companies, that derive a greater portion of revenues from high-margin pharmaceutical sales or royalties, enjoy slightly higher gross margins on average than branded pharmaceutical companies that are likely diversified into lower-margin businesses like medical devices and consumer products.

Figure 18: Average Gross Margins, Quarterly

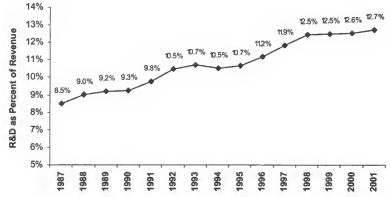


Sources: Bloomberg and analyst models.
Note: Gross margins are calculated as a percent of product sales, excluding all revenue associated with royalties, etc.

Research and Development Cost

As discussed earlier, the pharmaceutical industry depends on innovative research and development (R&D) to produce new medical treatments that are the key drivers for long-term growth. One useful measure of R&D across companies of different sizes is the amount of R&D spending relative to the amount of the company's total revenues. The average branded pharmaceutical company spent 8.5% of revenues on R&D in 1987 and over 12% in 2001, as shown in Figure 19. Although the change as a percent of revenues may appear small, the absolute dollar change for these nine companies was $3.8 billion in 1987 to $22.4 billion in 2001. These figures reflect overall R&D spending, which includes R&D costs for non-pharmaceutical businesses such as medical devices and consumer products.

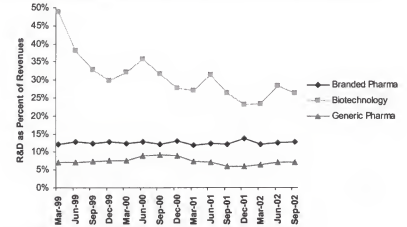
Figure 19: R&D as Percent of Revenue for Branded Pharma, Annual



Source: Bloomberg.

Since mid-2001, quarterly analysis shows that branded pharmaceutical companies, on average, have devoted a slightly increasing percentage of revenues to R&D efforts. This has happened due to both slightly higher R&D spending and slightly lower revenues due to generic entry.

Figure 20: Average R&D as Percent of Revenues, Quarterly



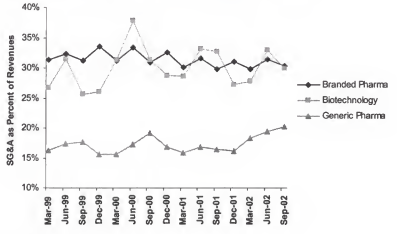
Sources: Bloomberg and analyst models.

The FDA does not require generic drug applicants to conduct separate, clinical trials to demonstrate a drug's safety and efficacy. As a result of having to conduct only bioequivalence studies, and not full clinical studies, generic pharmaceutical companies spend much less on R&D, both in absolute dollar terms as well as a portion of overall revenues. Some generic drug companies have increased internal R&D in an effort to launch more branded products of their own, a strategy which generally provides higher profit margins and better visibility for long-term growth than the traditional generic pharmaceutical business. Biotech companies, on the other hand, often are engaged in higher-risk, higher-reward clinical research. Due to their comparatively smaller revenue bases, biotech companies therefore spend a much higher percentage of revenue on R&D compared to their pharmaceutical counterparts. As product sales for biotech companies grow, however, the relative spending on R&D typically declines over time.

Selling, General, & Administrative Cost

In 2001, the average branded pharmaceutical company spent 31% of revenues for selling, general, and administrative (SG&A) expenses. SG&A includes marketing expenses, but very few companies break out the advertising and promotion component of this expense item. SG&A expense for the average biotechnology company was a similar 28%, while unsurprisingly much less for the average generic pharmaceutical at 15% of 2001 revenues.[13] The relative difference in SG&A as a percent of revenues for branded pharma, biotech, and generic pharma are shown below.

Figure 21: SG&A as Percent of Revenues, Quarterly



Sources: Bloomberg.

Because promotional spending is lumped together with the salary and overhead costs for the non-R&D functions, it is tremendously difficult to tease apart the financial data provided by the companies. Other sources of information, however, including IMS Health, detail promotional spending that gives some sense of overall industry spending. Promotional spending is generally broken down into three types: direct-to-consumer (DTC) advertising, physician advertising and detailing, and providing free drug samples. Between 1996 and 2000, total promotional spending has rose over 14%, with DTC advertising having grown the fastest.

[13] Generic drugs are typically not promoted by their manufacturers, but may be promoted by managed care companies encouraging use of less costly generic alternatives. In August 2002, FDA also began an educational campaign aimed at consumers about the safety and efficacy of generic drugs.

Figure 22: Promotional Spending by Pharmaceutical Manufacturers, 1996-2000

($ in millions)

Promotional Activity	Average Annual Percent Change 1996-2000	Percent of Total Promotion 1996	1997	1998	1999	2000
Free Samples	12.8%	53.5%	55.0%	52.7%	52.1%	50.6%
Detailing	12.4%	32.8%	30.6%	32.5%	31.1%	30.6%
Direct-to-Consumer Advertising	32.9%	8.6%	9.7%	10.6%	13.3%	15.7%
Professional Journal Advertising	1.4%	5.0%	4.6%	4.0%	3.4%	3.1%
Total Promotion	14.4%	100.0%	100.0%	100.0%	100.0%	100.0%
Total Promotion Spending		$9,164.3	$10,990.6	$12,473.8	$13,897.6	$15,708.2

Sources: IMS Health, Integrated Promotion Service, and Competitive Media Reporting, 1996-2001, as quoted by Kaiser Family Foundation.
Note: Includes activity of manufacturers of all prescription products, including branded pharmaceutical, biotechnology, and generic pharmaceutical companies. Sampling = the value of samples left at sales visits to office-based physicians. The samples are valued at the price they would be sold in retail pharmacies. Detailing = expenses for sales activity of pharmaceutical representatives directed to office-based and hospital-based physicians. Approximately 83% of this spending is for office-based sales visits. Direct-to-Consumer Advertising = expenditures for magazine, newspaper, radio, and television advertising targeted toward consumers. Professional Journal Advertising = expenditures for advertising prescriptioo products in medical journals.

Sampling cost, as measured by IMS, is the retail value of samples, not by the manufacturing cost of the drug samples.

The bulk of promotional spending is for sampling, or giving free drug samples directly to physicians. Physicians may distribute these free samples to patients, who otherwise would need to order the drugs from a pharmacy and typically would pay some out-of-pocket cost to fill prescriptions. In Figure 22, sampling cost is measured by the retail value of samples left at physicians' offices, not by the manufacturing cost of the drug samples.

Doctors and drug manufacturers have each adopted a new marketing code of ethics.

Detailing is the direct promotion of drugs to physicians. It is a primary method of providing education to physicians on new drugs and procedures. This takes place in physician's offices, hospitals, or other sites of care. This also includes promotional activities at major medical conferences. In 2002, the American Medical Association and the branded pharmaceutical industry trade group PhRMA each voluntarily adopted a new marketing code of ethics that restricted previous marketing practices such as complimentary trips, sporting event tickets, free tanks of gas, and rounds of golf.[14]

DTC advertising has been the fastest growing component of promotional expenditures of drug companies, particularly since the institution of 1997 FDA rules governing disclosure of side effect information on broadcast mediums like television and radio where "fine print" is economically less feasibly than in print.[15] The controversy over DTC stems from arguments that DTC advertising expenses add to prescription drug spending and drive inappropriate utilization. Data from the National Ambulatory Medical Care Survey (NAMCS) has shown that the number of physician visits that included at least one new or continued medication to be ordered, supplied, or administered has risen to 66.1% in 2000 compared to 63.4% in 1997. The number of times drugs are mentioned per 100 physician visits has also risen from 130.9 mentions in 1997 to 153.4 in 2000.

IMS Health has found that three-fourths of total prescription drug spending increases in 2000 were driven by utilization of new medicines and increased use of existing medicines, while price increases on existing medicines accounted for the remaining one-fourth of prescription drug cost increases. A recent GAO report found that between 1999 and 2000, the number of prescriptions dispensed for the most heavily advertised drugs rose 25%, but increased only 4% for drugs that were not heavily advertised. Over the same period,

[14] On September 30, the HHS Inspector General issued draft compliance guidance that highlighted certain marketing practices that could raise red flags by enforcement officials, including kickbacks and other illegal remuneration, compliance with laws regulating drug sampling, and integrity of pricing data used by Medicare/Medicaid in setting reimbursement.

[15] In addition to the approval and monitoring of prescriptioo drugs, the FDA also regulates the promotioo of prescription drugs, including contont of DTC advertisements, under the authority of the Federal Food, Drug and Cosmetic Act (FFDCA). Under current regulations, pharmaceutical companies are required to submit all drug advertisements to FDA at the same time they are released to the public. In 2001, FDA reviewed 248 broadcast advertisements and unknown number of DTC priot advertisements. Although FDA does not pre-approve DTC advertisements, the agency does accept voluntary submission of materials before launch, and gave advisory comments on 128 broadcast advertisements in 2001.

prices rose 6% for the most heavily advertised drugs and 9% for the others. Advertising is unlikely the sole reason for increased drug utilization; other factors such as improved efficacy or expanded market size could also explain increased utilization of drugs that were being heavily promoted.

Figure 23: Prescription Drugs with the Most Direct-to-Consumer Advertising, 2000

($ in millions)

Drug	Indication	DTC Promotion Spending	Top 200 Sales Ranking
Vioxx	Anti-inflammatory	$160.8	20
Prilosec	Anti-ulcerant (PPI)	107.9	5
Claritin	Antihistamine	100.3	9
Paxil	Anti-depressant (SSRI)	92.1	14
Zocor	Cholesterol-lowering	91.2	17
Viagra	Erectile Dysfunction	89.8	45
Celebrex	Anti-inflammatory	78.8	11
Flonase	Asthma	78.1	50
Allegra	Antihistamine	67.0	31
Meridia	Weight-loss	65.0	NR
Total DTC Promotion Spending		$2,467.1	

Sources: Competitive Media Reporting, Strategy Report, and IMS Health, National Prescription Audit Plus, as quoted by Kaiser Family Foundation.

Drug companies spend more on R&D than on promotional activities.

According to industry estimates, in 2001, pharmaceutical companies spent $30.3 billion on R&D, compared to $19.1 billion on all promotional activities (including $2.7 billion for DTC advertisements). A recent GAO report stated that between 1997 and 2001, DTC advertising spending increased 145%, while R&D spending increased 59%. Total promotional spending was equivalent to 12% of drug sales in the U.S. in 2001.

Nearly half of physician CME is funded by the drug industry.

In addition to direct promotional costs that are audited by IMS, pharmaceutical manufacturers also fund much of the medical profession's continuing medical education (CME) courses. Most states require physicians to participate in CME courses to maintain their medical licenses. CME courses and events are provided by a variety of sources: medical schools, medical societies, hospitals, foundations, health associations, and companies that specialize in medical communications, education, and publishing. In 2001, $569 million or 48% of the $1.2 billion spent on CME was funded by industry sources, which include pharmaceutical and medical device manufacturers. If other conference exhibit and related advertisement costs are included, industry funded $769 million or 62% of spending on CME programs. Despite its funding source, CME courses must be accredited by a third-party and drug companies cannot control course preparation, delivery, or content. CME courses can include certain types of information that cannot be promoted by drug sales representatives, such as off-label uses or efficacy information on investigational drugs.

ACCESS TO CAPITAL

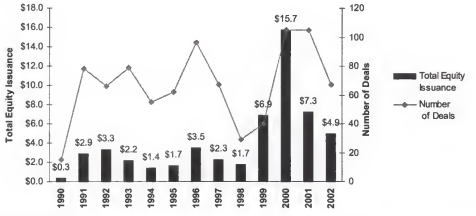
Equity and Debt Issuance

Large pharmaceutical manufacturers often generate sufficient cash flow to fund capital needs.

Capital sources include the equity and debt markets. Large pharmaceutical manufacturers may choose to tap into the public debt and equity markets, especially when funding acquisitions or refinancing existing debt. They are, however, often able to generate strong cash flow to fund a significant amount of their capital needs. It is more common to see rapidly growing smaller pharmaceutical manufacturers and biotechnology companies issue debt and equity for their capital needs. Figures 24 and 25 show the equity and debt issuance for the entire pharmaceutical and biotechnology industries since 1990. Both the number of deals and amount of equity issued peaked in 2001, while the issuance of debt peaked in 2001.

Figure 24: U.S. Equity Issuance for Pharma and Biotech Industries, 1990-2002 YTD

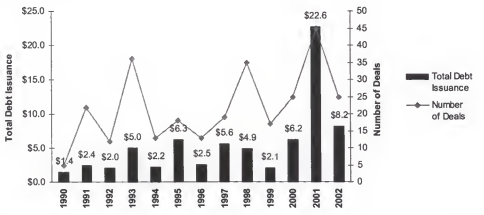
($ in billions)



Sources: SDC and JPMorgan.
Note: Includes public, private, and 144A common stock offerings for pharmaceutical or biotechnology companies by Securities Data Corporation. As of December 5, 2002.

Figure 25: U.S. Debt Issuance for Pharma and Biotech Industries, 1990-2002 YTD

($ in billions)



Sources: SDC and JPMorgan.
Note: Includes public, private, 144A, convertible and non-convertible debt offerings for pharmaceutical or biotechnology companies by Securities Data Corporation. As of December 5, 2002.

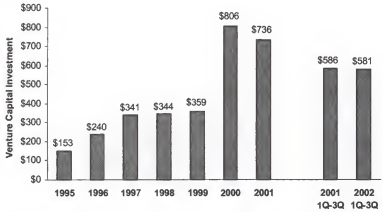
Venture Capital

Venture capital is a type of private equity investment that historically has played a vital role in funding and helping develop young R&D-based companies, such as biotechnology companies and medical device companies. Venture capital funds invest in relatively early-stage, high-risk companies. Unlike large pharmaceutical or biotechnology companies that generate positive cash flow to fund operations, small companies that have not reached profitability often rely on this private equity in order to provide cash flow for continued operations.

As seen in Figure 26, biotechnology venture capital reached its peak in 2000, with over $800 million of venture capital investment in one year alone, up 124% from the previous year. Although venture capital financing has been declining since peaking in 2000, investment through the third quarter of 2002 showed no change from the first three quarters of 2001.

Figure 26: Venture Capital Investment in Biotechnology, 1995-2002 YTD

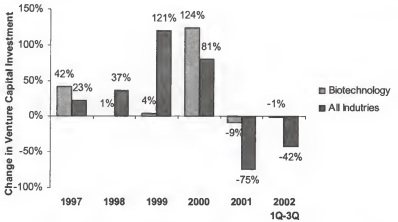
($ in millions)



Source: PricewaterhouseCoopers/Thomson Venture Economics/National Venture Capital Association MoneyTree Survey.
Note: 2002 year-to-date figures are as of September 30, 2002.

The graph below shows that although venture capital spending saw a steep decline in 2001, this decline was weathered better by biotech than total venture capital investment in all industries. While the total level of venture capital spending peaked in 1999, the boom in biotechnology spending did not occur until 2000, with excitement fueled by developments such as the sequencing of the human genome in late 1999.

Figure 27: Changes in Venture Capital Investment, 1996-3Q 2002



Source: PricewaterhouseCoopers/Thomson Venture Economics/National Venture Capital Association MoneyTree Survey.
Note: Third quarter 2002 figures are as of September 30, 2002.

Industry sources suggest that both the capital markets and venture capital financing boom of 2000 left many biotechnology companies with healthy cash positions to continue funding of research and development. As seen in Figure 28 below, at the end of 1999, 55% of publicly traded biotech companies had less than two years' of cash, and 36% had less than one year's worth. At the end of 2000, 54% had at least three years of cash, and 42% had more than five years. This trend also reflects newly public companies that were enriched by initial public offerings, as the number of public biotech companies increased from 301 in 1999 to 339 in 2000.

Figure 28: Cash Positions of Publicly Traded Biotechnology Companies, 1999-2000

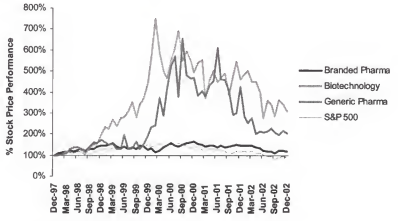
	1999		2000	
	Number of Companies	Percent of Total	Number of Companies	Percent of Total
More than 5 year's cash	76	25%	143	42%
3-5 year's cash	29	10%	40	12%
2-3 year's cash	30	10%	27	8%
1-2 year's cash	59	20%	57	17%
Less than 1 year cash	107	36%	72	21%
Total Public companies	301		339	

Source: Company financial statements, as analyzed by Ernst & Young.

Stock Market Performance

Stock market performance is often viewed as a quantitative reflection of future expectations for risk and reward. Successful market performance can increase the ability of a company to raise capital by issuing stock, an important issue for smaller biotechnology companies. Over the past five years, the branded pharmaceutical, biotechnology, and generic drug industries have all outperformed the S&P 500. High-growth stocks like biotechnology and generic drug stocks benefited in 1999 and 2000, particularly after the sequencing of the human genome in the autumn of 1999. In comparison, the branded pharmaceutical stocks were relatively flat. This is shown in Figure 29.

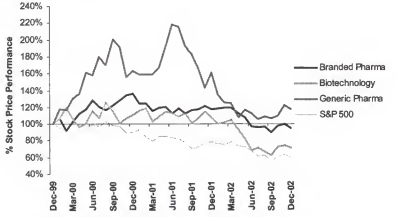
Figure 29: Relative Stock Market Performance Over 5 Years



Source: Bloomberg. As of December 31, 2002.
Note: Indices are market-cap weighted.

Since 2000, biotechnology companies have fared comparatively worse, as expensive valuations came down rapidly. Generic companies continued to enjoy record profits due to a number of patent expirations, but also began suffering in mid-2001. Both the branded and generic drug sectors fared better than the biotech sector with strong profits and healthy cash flows. Although the pharmaceutical sector typically is considered to be "defensive" during uncertain economic times, a series of manufacturing compliance issues, regulatory delays, and inventory management problems caused a series of unexpected earnings shortfalls and have clouded earnings visibility, punishing sector performance over the past year.

Figure 30: Relative Stock Market Performance Over 3 Years



Source: Bloomberg. As of December 31, 2002.
Note: Indices are market-cap weighted.

Figure 31: Company Stock Market Performance

Company Name	Stock Perforamnce 5-Year	3-Year	1-Year
U.S. Branded Pharma			
Abbott Laboratories	122%	110%	72%
Bristol-Myers Squibb Co	51%	38%	45%
Johnson & Johnson	163%	115%	91%
Eli Lilly & Co.	91%	95%	81%
Merck & Co, Inc	107%	84%	96%
Pfizer Inc	123%	94%	77%
Pharmacia Corp	106%	125%	104%
Schering-Plough Corp	71%	52%	62%
Wyeth	98%	95%	61%
Biotechs			
Amgen Inc	357%	80%	86%
Biogen Inc	220%	47%	70%
Cephalon Inc	428%	141%	64%
Chiron Corp	221%	89%	86%
Genentech Inc	93%	49%	61%
Genzyme Corp	221%	131%	49%
Idec Pharmaceuticals Corp	579%	101%	48%
Medimmune Inc	380%	49%	59%
Generic Pharma			
Andrx Corp	171%	69%	21%
Barr Laboratories Inc	286%	311%	82%
Ivax Corp	337%	88%	60%
Mylan Laboratories	167%	139%	93%
Watson Pharmaceuticals Inc	87%	79%	90%

Source: Bloomberg. As of December 31, 2002. Figure excludes Immunex (acquired by Amgen in 2002).

Merger and Acquisition Activity

According to Carl Seiden of JPMorgan, major mergers between pharmaceutical companies have occurred at a rate of about one per year for the last fifteen years. He notes, "Historically, the catalyst for major M&A among drug companies has primarily been fear and pain relative to earnings." The last big wave of mergers followed the difficult years for the drug industry in 1992 to 1994. During 1994 six deals were announced: Roche/Syntex, AHP/American Cyanamid, Glaxo/Wellcome, Hoeschst/Marion Merrell Dow, Pharmacia/Upjohn, and Novartis/[Ciba/Sandoz]. The largest transactions in the past few years include Pfizer/Warner-Lambert, Pfizer/Pharmacia (still pending regulatory approval), and Glaxo/SmithKline Beecham. Each merger prompts debate over the question of whether "bigger is better," as mergers create enormous marketing and R&D infrastructures and budgets.

Because the industry remains highly fragmented, analysts continue to speculate over whether there will be a new wave of M&A activity. By combining two companies, synergies can cause the efficient financial operation of the combined company as duplicative cost structures (*e.g.*, SG&A and R&D) are eliminated. Seiden notes:

> The ability to cut (on average) 20% of the cost base of the acquired company (range is 5-11% of combined costs) is well established, and generally boosts the value of the acquired company's earnings flow by 40-50% or more over the three-year period of the cuts....The financial logic generally gives a nice ride to shareholders (depending of course on deal structure and size) and buys management time (after which they may have gotten to a "better pipeline," or have even greater challenges to growth).

In addition to expense-related synergies, complementary product portfolios with similar therapeutic uses can create revenue synergies as the combined company seeks to dominate a particular therapeutic platform, and sold by a numerically (and often geographically) larger sales force. Investors, however, view the primary driver of M&A in this industry as the need to identify future sources of earnings growth when internal pipelines seem dry. Although less predictable, internal R&D efforts can be supplemented through transactions such as purchasing another company with a pipeline of its own, or licensing agreements.

Pharmaceutical companies that look to fill pipeline gaps also look to acquire (or negotiate licensing deals with) smaller pharmaceutical or biotechnology companies. The large pharmaceutical companies can often offer steady funding, increased manufacturing capacity, deeper distribution, and more experience in regulatory and payment processes compared to their smaller partners. Kenneth Kulju of Credit Suisse First Boston estimates that one in five new molecular entities is developed by the biotechnology sector. He notes, "We are anticipating increasing alliance activity by the major pharma sector with the biotechnology industry, with biotech's more nimble size, rapid decision making structures, and more, innovative, less risk-adverse cultures appearing more appropriate for new discovery initiatives." In addition, biotech companies are now receiving better economic terms for such mergers or collaborations. Terms have improved due to a limited supply of late-stage development products in both the pharmaceutical and biotechnology pipelines.

The biotechnology sector itself has undergone several major mergers in recent years. Several key biotechnology product launches in the late 1990s, combined with a record amount of capital raised in 2000, left the industry with record revenues, newfound profits, and strengthened balance sheets. For the first time, biotech companies had the ability to both continue funding research and development as well as acquire companies. Major mergers that occurred during this time were Amgen/Immunex, Millenium/Cor Therapeutics, and MedImmune/Aviron. These mergers have created biopharmaceutical companies with diversified revenue bases and global sales forces, which are beginning to approach the size of the more mature pharmaceutical companies.

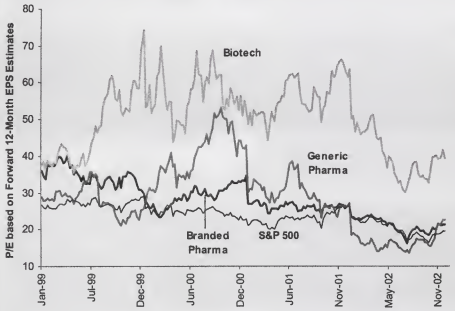
The trend towards globalization of the pharmaceutical industry has also driven consolidation, particularly for non-U.S. based pharmaceutical companies. Non-U.S. companies tend to be more exposed to international markets, where margins are lower often due to mechanisms such as price controls. In the effort to increase participation in the U.S. market, non-U.S.-based companies may choose to acquire or merge with U.S.-based companies that have an established U.S. sales and distribution infrastructure. This trend towards increasing sales infrastructure also drives mid-sized U.S. pharmaceutical companies to partner or merge with their larger counterparts, that may desire access to the smaller companies' products or technology. Stephen Scala of SG Cowen writes:

> [H]igher costs of remaining competitive in marketing and R&D will drive continued merger and acquisition activity, likely involving non-U.S. companies, which are disproportionately exposed to weaker markets, mid-sized companies looking to expand marketing and development infrastructures, and larger companies with pipeline gaps.

P/E Multiples

One simple valuation measure used by analysts and investors is the price-to-earning (P/E) ratio or multiple. A P/E multiple shows what the market is willing to pay for a company's stock as a multiple of the earnings that the company generates. (To calculate P/E, divide the price per share by the annual earnings per share.) P/E multiples can provide relative valuations between companies within the same industry. Similarly, industry average P/E multiples can also be used to compare relative valuations between sectors. P/Es tend to show that investors pay more for stocks with greater confidence in higher earnings expectations. Since 1999, the average P/E for the branded pharmaceutical companies was 28x, 50x for biotech, 29x for generic pharmaceutical, and 24x for the S&P 500.

Figure 32: Comparison of Average P/E Multiples, 1999-Present



Sources: JPMorgan and FactSet.
Note: P/Es not based on full-year of profitability are excluded.

REVENUE SOURCES

The private sector shouldered over three-quarters of retail prescription drug costs in 2001. Private insurance pays for 47% of national retail drug spending, while out-of-pocket payments account for 31%. Pharmacy benefits for Medicaid, a federal-state partnership, vary in design from state to state, and accounted for 17% of spending. Medicare offers comparatively little coverage of outpatient drugs, accounting for less than 2% of spending but still translating into $2.4 billion in retail sales. This figure excludes Medicare payments for drugs provided through non-retail channels, such as hospitals and physicians' offices. In 2001, Medicare spent over $7 billion for outpatient drugs. Other public sector programs, including the Veterans' Administration and Department of Defense, incur the remainder of public drug spending.

Figure 33: Retail Prescription Drug Spending by Payor

($ in billions)

	National Expenditures	Percent Share	Growth 2000-2001
Retail Prescription Drug Spending	$140.6	100%	16%
Private	$109.7	78%	16%
Out-of-pocket	43.1	31%	13%
Insurance	66.6	47%	17%
Public	$30.8	22%	16%
Federal	17.6	13%	15%
Medicare	2.4	2%	4%
Medicaid	14.2	10%	16%
Other	1.0	1%	33%
State & Local	13.2	9%	16%
Medicaid	10.3	7%	15%
Other	2.9	2%	18%

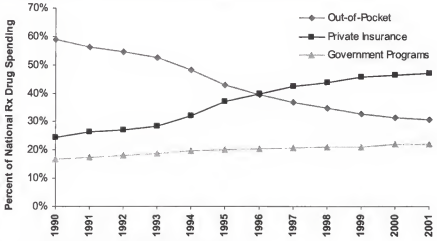
Source: CMS, Office of the Actuary, National Health Statistics Group.
Note: Medicare prescription drug spending in this table excludes payment for drugs provided through non-retail channels, such as hospitals and physicians' offices.

Private Payors

Private Insurance

In the 1970s, prescription drugs were typically not covered under the then-popular fee-for-service plans. In the late 1970s, prescription drugs accounted for only 5% of national health expenditures, and thus most insurers did not include coverage and drug costs were paid for out-of-pocket. The rise of managed care in the 1980s allowed patients to pay a relatively small $5 or $10 co-pay when purchasing drugs. Thus, while out-of-pocket costs stayed low for the beneficiary, utilization and demand for prescription drugs skyrocketed. This trend increased both drug costs as a percent of national health expenditures and also shifted out-of-pocket drug costs to private insurance, which continued into the next decade. In 1991, private insurance accounted for 26% of $45 billion in retail drug spending; in 2001, private insurance accounted for 47% of $141 billion in retail drug spending, as shown in Figure 34.

Figure 34: Trends in Sources of Prescription Drug Spending



Source: CMS, Office of the Actuary, National Health Statistics Group.

Managed care plans have adopted tiered formularies.

Although pharmacy benefits differ, most managed care plans rely on the use of formularies, or lists of prescription drugs approved for insurance coverage. "Open" formularies reimburse for both listed and non-listed drugs, while "closed" formularies reimburse only listed drugs. A majority of managed care plans have adopted tiered formularies, which require escalating out-of-pocket co-payments for generic, preferred branded, and non-preferred branded drugs. This gives the patient an economic incentive to control drug spending. In 2002, 55% of formularies had three tiers, 30% had two tiers, and only 15% had one tier.

Many managed care organizations use pharmacy benefit managers (PBMs) to design and administer prescription drug benefits for their members. PBM services include management of drug formularies and negotiation of discounts from drug manufacturers through volume-based purchasing. PBMs are not actual purchasers of drugs, but intermediaries that leverage managed care company's volume purchasing power to negotiate lower costs. The top four PBMs manage approximately 54% of U.S. pharmaceutical sales.[16] PBMs often also manage claims processing, pharmacy benefit cards, preferred pharmacy networks, mail order, and formulary lists. While PBMs have undoubtedly played an important role in containing drug costs, actual cost-savings data is difficult to collect because price discounts are closely guarded as competitive information.

While there are several large independent PBMs, many are owned by larger managed care organizations. PBM subsidiaries do not compete for outside business but internally manage prescription benefits for health plan members. Likewise, retail pharmacy chains can own their own PBMs, which are usually much smaller than the independent PBMs. During the early 1990s, many pharmaceutical manufacturers felt it was necessary to acquire a PBM to stay competitive, but this strategy came under regulatory scrutiny, out of concern that formulary decisions would be unfairly influenced by the parent company's drug portfolio, and the FTC established firewalls between the two businesses.[17]

[16] While payors provide some overall discretion or design parameters, formulary decisions are usually made by a PBM's pharmacy & therapeutics (P&T) committee which is comprised of independent physicians and pharmacists who review the clinical effectiveness of each drug, and then evaluate them based on pricing information. PBMs then negotiate with manufacturers for rebates and discounts.

[17] In 1993, Merck, SmithKline Beecham and Eli Lilly each acquired a PBM, but SmithKline and Lilly divested their PBMs in the late 1990s, and Merck intends to do the same.

The Pharmaceutical Distribution Chain

When filling a prescription, most consumers are unaware of the complicated chain of manufacturers, suppliers, and payors involved in pharmaceutical distribution. Pharmaceutical manufacturers sell approximately 70% of their drugs to wholesalers and the remaining 30% directly to pharmacies and self-warehousing chains. The dollar flow in a typical private payor scheme is explained below.

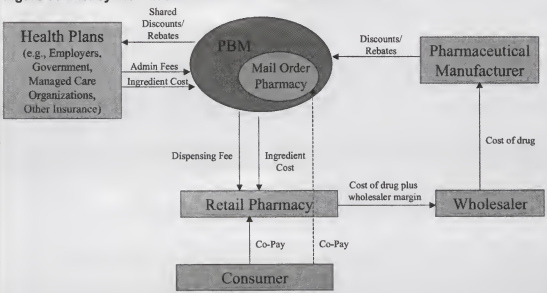
A customer fills a prescription at a retail pharmacy and pays a co-pay amount to the pharmacy according to his or her insurance plan. Retail pharmacies usually purchase inventory from a wholesaler that purchases directly from the pharmaceutical manufacturer. The pharmacy sends a bill to the pharmacy benefit manager (PBM), which covers the balance of the ingredient cost plus a dispensing fee. Both are pre-negotiated amounts. Dispensing fees depend on the amount of volume the PBM can drive to the pharmacy. For example, a dispensing fee might be $2 for a brand-name drug and $3 for a generic, which encourages generic substitution. PBMs usually negotiate an ingredient cost with the pharmacy based on a discount to the average wholesale price (AWP). The maximum ingredient cost is usually limited to the "usual & customary" price, or the price charged to a cash-paying customer.

The PBM then sends the bill to the health plan, which reimburses the PBM for the ingredient cost, dispensing fee, and transaction fee for claims processing and other administrative tasks. The PBM retains these administrative fees, typically around 1% to 3% of the wholesaler acquisition cost, and reimburses the pharmacy for the ingredient cost plus the dispensing fee, minus the co-pay.

If the customer fills a prescription through a mail order pharmacy, the customer pays a co-pay amount to the mail order pharmacy, which is typically part of the PBM itself. The PBM usually purchases inventory for its mail order pharmacy directly from the pharmaceutical manufacturer. The PBM then sends the bill to the health plan to cover the ingredient cost and transaction fee. After receiving the claim from the health plan, the PBM then reimburses the distributor or manufacturer for the ingredient cost of the drug.

Analyzing these transactions, the manufacturer and the PBM can see what effect the PBM had on driving market share of certain drugs and will pay rebates to the PBM accordingly. The PBM can then pass on a percentage of these rebate dollars to the health plan sponsor to reduce the health plan's total drug costs.

Figure 35: Money Flow In the Pharmaceutical Distribution Chain

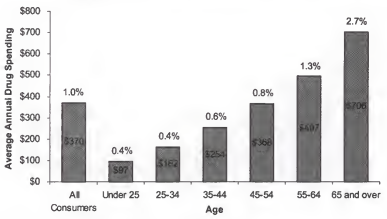


Source: CMS, Office of Research, Development, and Information.

Individuals

The average American spent $449 out-of-pocket for drugs, or 0.9% of his or her income, in 2001. The average out-of-pocket spending in terms of dollars and as a percent of income clearly rises with age, as shown in Figure 36 below. Senior citizen out-of-pocket drug costs have been rising rapidly. In 2001, the average senior citizen spent $884 out-of-pocket for drugs, or 3.2 % of his or her income, compared to the average $444 or 2.2% in 1991.

Figure 36: Average Out-of-Pocket Drug Expenditures, Dollars & Income Percentage, by Age



Source: Bureau of Labor Statistics, Consumer Expenditure Surveys 2001.
Note: Drug spending includes prescription drugs, non-prescription drugs, and vitamins.

Those without prescription drug insurance pay higher prescription drug prices than those who are insured.

Uninsured

A study by the Department of Health and Human Services found that in 1999, cash customers paid nearly 15% more than customers with prescription drug insurance. For 25% of the most commonly prescribed drugs, this price difference was even higher—over 20%. The pharmaceutical industry has begun to respond to the increasing drug needs and financial limitations of Medicare beneficiaries. While Congress continues to debate a legislative prescription drug benefit, many major pharmaceutical companies have introduced prescription drug discount card programs. Programs vary in terms of eligibility and discounts, but most offer discounts based either on a flat cost per prescription or a percent discount from the average wholesale price (AWP), and are offered to Medicare beneficiaries with no drug coverage and an annual income cap that is typically two to three times the federal poverty level.

Public Payors

Medicare

Medicare pays for drugs administered in inpatient hospital and nursing home settings under bundled payment rates but does not pay for most outpatient prescription drugs.[18] Medicare does, however, cover a limited number of drugs that are typically provided in hospital outpatient settings, dialysis centers, or doctors' offices, and are purchased directly by the physician or physicians and providers. Drugs covered by Medicare include:[19]

- Drugs that are not usually self-administered and furnished incident to a physician's service, such as some chemotherapy drugs
- Certain oral cancer and anti-nausea drugs
- Certain drugs used in conjunction with certain durable medical equipment or infusion devices, (*e.g.*, albuterol used in nebulizers, which are devices used by asthma patients)
- Immunosuppressive drugs, when used for organ transplant patients
- Clotting factors for beneficiaries with hemophilia
- Epoetin alpha, which is used primarily to treat anemia in end stage renal disease patients and in cancer patients, constitutes Medicare's largest drug expenditure (approximately $2 billion)
- Osteoporosis drugs injected into certain beneficiaries by home health agencies
- Certain vaccines (by statute), such as for influenza, pneumonia, and hepatitis B

Under the outpatient prospective payment system, there are approximately 450 covered drugs, but about 35 drugs account for 92% of prescription drug spending and 95% of Medicare claims.

Medicare Coverage Determination Process

While the FDA approves a drug for marketing if it is safe and effective, CMS, on the other hand, acts as an insurer and determines whether it is appropriate for Medicare to *pay* for a drug. The agency does this through its coverage determination process in which a new drug is examined to determine whether it improves net health outcomes in Medicare beneficiaries as well as or better than other available therapies and warrants expenditure of taxpayer dollars.

Local Coverage Determinations

Most Medicare coverage decisions are made at the local level by Medicare contractors.

The majority of coverage decisions are made at the local level by Medicare contractors: fiscal intermediaries that process claims from facilities and carriers that process claims from physicians and labs. To allow for regional differences in medical practice, Medicare allows contractors some flexibility in making coverage decisions. Most new drugs are paid without specific review by contractors. Coverage for a specific drug may be determined on a case-by-case basis if the new drug is brought to the contractor's attention or if the contractor becomes aware of the new drug when reviewing trends in previously paid claims. If there is an unusually high volume of high-cost claims or denials for a

[18] Throughout this discussion, the term "drugs" should be assumed to include both drugs and biologicals unless otherwise specified.

[19] Medicare covers drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them, as amended by BIPA 2000. Medicare interprets the clause "not usually self-administered" to mean injectable (including intravenous) drugs that are not usually self-administered by more than 50% of those Medicare beneficiaries who use the drug. Although coverage is determined locally by the fiscal intermediaries and carriers, CMS has provided guidance that intravenous drugs and intramuscular injections should be presumed to be not usually self-administered, while subcutaneous injection should be presumed to be usually self-administered, absent evidence to the contrary.

specific drug (or medical device or service), the contractor may issue a local medical review policy (LMRP). During the LMRP development process, a contractor gathers and examines the clinical evidence and determines whether the item or service: 1) has a benefit category, 2) is not statutorily excluded, and 3) is reasonable and necessary. The contractor usually posts the draft LMRP for 45 days of public comment, reviews these comments and any new data, and finally, posts the final LMRP. During the development of most LMRPs, carriers are required to consult with the Carrier Advisory Committee (CAC), a panel of local physicians. Fiscal intermediaries generally develop their LMRPs with input from medical providers and organizations. In addition, all contractors ask for public comment and hold open meetings to discuss their draft LMRPs. Effective October 1, 2002, each contractor must develop an LMRP reconsideration process to allow beneficiaries and providers to submit suggested revisions to LMRPs along with clinical evidence that supports the change.

National Coverage Determinations

National Coverage Determinations (NCDs) are triggered by the manufacturer or by CMS when a universal policy is necessary.

A National Coverage Determination (NCD), which supercedes local policies, is triggered by either the request of an outside party (typically the manufacturer) or by CMS. In the absence of an external request, CMS generally initiates an NCD when the item or service raises significant scientific issues, could have a substantial impact on the Medicare population, or there are major variations in local policies. CMS conducts a complete evidence-based review to determine if the item or service is clinically effective and therefore, reasonable and necessary. At the beginning of each NCD, CMS posts a tracking sheet and allows for 30 days of comment to be reviewed during the decision process. Each NCD includes a complete technology assessment process, including collection and careful evaluation of all relevant data. For some NCD assessments, CMS requests external assistance and/or the independent review of the Medicare Advisory Committee (MCAC). A Decision Memorandum is posted to summarize the analysis and inform the public of the intent to implement the policy decision. The NCD process currently allows as many as 270 days between the issuance of an NCD and the deadline by which individual Medicare contractors must reflect the coverage decision in their processing systems.

Medicare Payment for Drugs

Medicare Payment for Physician-Administered Drugs

Medicare pays for covered drugs administered incident to physicians' services. These payments are made to physicians through carriers, contractors to the Medicare program. Carrier payment to physicians for drugs is based on the lower of the billed charge or 95% of the average wholesale price (AWP). AWP is a CMS-determined price identifier. CMS presently identifies AWP as listed in industry compendia such as the *Red Book*.[20]

For calendar year 2001, the top 25 drugs paid for by Medicare carriers accounted for about 80% of all Medicare carrier drug spending. Medicare carriers' total allowed charges for all drug expenditures was approximately $6.4 billion in 2001, including deductible and co-payments paid by beneficiaries. This does not include drug expenditures paid by fiscal intermediaries, which includes over $1 billion in Medicare payments for Epogen. The relative percent of total Medicare carrier drug spending for the largest drugs are shown below.

[20] For more on AWP, please see page 48.

Figure 37: Top Drugs by Medicare Carriers' Allowed Charges, 2001

($ in millions)

Drug Name (generic)	Main clinical uses	Company	Allowed Charges	% of Total
Procrit (epoetin alpha)	Anemia related to chemotherapy	Johnson & Johnson	$780	12.1%
Lupron (leuprolide)	Prostate cancer	TAP	$665	10.4%
Ipratropium (generic)	Asthma, COPD	Multiple	$470	7.3%
Zoladex (goserelin)	Prostate cancer	AstraZeneca	$437	6.8%
Albuterol (generic)	Asthma, COPD	Multiple	$351	5.5%
Rituxan (rituximab)	Non-Hodgkin's lymphoma	IDEC/ Genentech	$270	4.2%
Paclitaxel (generic)	Ovarian, breast, lung cancer	Bristol-Myers Squibb, multiple generics	$269	4.2%
Remicade (infliximab)	Rheumatoid arthritis, Crohn's disease	Johnson & Johnson	$196	3.1%
Aredia (pamidronate)	Hypercalcemia	Novartis	$193	3.0%
Taxotere (docetaxel)	Breast, lung cancer	Aventis	$168	2.6%
		Top 10 Drugs	**$3,802**	**59.2%**
		Total Carriers' Allowed Charges for Drugs	**$6,422**	**100.0%**
Epogen (epoetin alpha)	Anemia related to dialysis	Amgen	*$1,163	
		Total Allowed Charges for Drugs plus Epogen	**$7,586**	

Source: CMS, Center for Medicare Management.
Note: Medicare carrier allowed charges include deductible and premiums paid by beneficiaries.
* Medicare payment for Epogen is estimated for 2001. This estimate of Medicare spending for Epogen applies only to fiscal intermediary payments.

Prospective Payment Systems

For drugs administered in the inpatient and outpatient hospital setting, Medicare pays bundled rates for care provided to beneficiaries under its various prospective payment systems (PPSs).

Medicare pays bundled rates for procedures—not for the provider's acquisition cost of a specific drug.

A PPS encourages providers to operate efficiently by paying the same base amount to all providers for similar cases. The base rate in each PPS is adjusted for several factors. Some factors are common across PPSs (*e.g.*, geographic differences in costs) while others are unique to an individual PPS (*e.g.*, an adjustment for physician medical education in the inpatient PPS). Provider costs vary from case to case. The bundled payment rate is based upon the average resources required to treat a specific category of clinically similar patients relative to the resources required to treat patients in other categories. In some payment systems, the relative cost is compared to the average cost for all patients in that payment system (*e.g.*, inpatient PPS) while in others the relative cost is compared to the average cost for patients in one "benchmark" category (*e.g.*, outpatient PPS). In both cases, it is expected that the gains providers incur for low-cost cases will offset losses for high-cost cases, assuming sufficient patient volume and mix. The resources required to complete treatment may include labor, facilities, malpractice insurance, pharmaceuticals, medical devices, and medical supplies. Expected resource utilization can vary because of the diagnosis, procedure(s) to be performed, or the relative acuity of each patient. Thus, the price that a drug manufacturer charges a hospital will likely be different from the payment the provider receives for the total case.

PPS Updates

As noted above, Medicare calculates the payments for each case based on the relative weight of resource utilization for the category in which the case is assigned compared to other cases. These relative weights are multiplied by a dollar amount (known as the standardized amount in the inpatient PPS and the conversion factor in the outpatient PPS) to calculate the actual payment for each case. These amounts are further adjusted for various factors that vary across payment systems.

Medicare PPS payments are reweighted annually.

Medicare PPSs are designed to be flexible over time—each payment classification is reweighted annually based on the most recently available claims information submitted by providers. Medicare analyzes claims information annually to account for changes in resource utilization. Changes in resource utilization may be due to a number of factors, including changes in the relative cost of providing services, changes in medical practice or technological improvements that result in price changes.

New drugs that represent incremental or marginal changes to existing technology and whose cost is similar to existing technology are almost always automatically covered by Medicare contractors as described above. New technologies that are significantly more expensive than existing technology may take more time to get additional costs recognized under Medicare's payment systems. (These new technologies may represent either incremental or substantial innovation.) These additional costs are sometimes offset by supplemental new technology payments, which are discussed below. Any delay in upward adjustment in payment on the front end for more expensive technologies, however, is often later offset by a delay in the reduction to payment on the back end. This occurs as the result of hospital acquisition costs declining over time due to market forces such as competition from other manufactures or provider adoption of even more advanced technologies. It is important to note that Medicare will almost always begin making some sort of payment once the technology is approved.

Figure 38 presents the requirements of the traditional Medicare coverage and payment process for the inclusion of new technology.

Figure 38: Medicare New Technology Coverage and Payment Process Requirements

In order to be covered and paid by Medicare, these five requirements must be met. The process for each may overlap and may vary in order.

- FDA approval:
  -Drug must be deemed safe and effective.
- Medicare benefit category decision:
  -Drug must fit into a benefit category defined by federal statute.
- Coverage:
  -Drug must be reasonable and necessary for the diagnosis or treatment of an illness or injury.
- Coding, the drug may be placed into a(n):
  -existing code
  -a temporary "catch-all" code
  -a new code
- Payment adjustments are made to:
  -Inpatient PPS
  -Outpatient PPS
  -other fee schedule

Source: CMS, Center for Medicare Management.

While the bundled payment amounts may not always fully reflect new technology cost, new devices and procedures can be reflected in and adjustments made to these bundled payments in as little as twelve months for the inpatient PPS and as little as four months in the outpatient PPS. There have been recent cases in which CMS has accelerated certain new technologies (such as drug-eluting stents) through this process in order to ensure faster beneficiary access to new technology.

Medicare Supplemental New Technology Payments

Historical claims data typically do not exist for a new drug. Under the inpatient and outpatient PPSs, Medicare calculates supplemental new technology payments to increase beneficiary access to new, more expensive technologies. Over time, Medicare uses actual hospital claims data to adjust payments of bundled rates, ending the use of supplemental payment for the device. This system can cause wide fluctuations in payment rates, especially during the early years of a new drug.

New Technology Special Add-on Payment in Inpatient PPS

In BIPA 2000, Congress instructed CMS to create procedures and criteria for new technology payments for inpatient prospective payment system (IPPS). These payments are capped at 1% of total IPPS spending. CMS set three new technology payment criteria for the new technology add-on payment, all of which must be met. The new technology must be:

1) new,
2) a substantial medical improvement relative to existing technology, and
3) of sufficient cost.

New drug utilization can affect other costs of the procedure.

To be eligible to receive any new technology add-on payment, the expected average charge for cases using the new technology must be greater than one standard deviation above the standardized average charge for all other cases in the diagnosis related group (DRG) to which the cases using the new technology would be assigned. CMS compares total charges for cases using new technology to other cases in the same DRG because a new technology can affect other costs of the procedure (*e.g.*, increased use of other supplies, decreased length of stay, etc.). If the new technology meets the three requirements above, for each case using the new technology CMS will pay the sum of: (a) the DRG payment for the DRG into which the case is assigned and (b) half of the difference between the DRG payment and the cost of the particular case using the new technology. If the actual costs of the new technology case exceed the DRG payment by more than the cost of the new technology, Medicare payment would be limited to the DRG payment plus 50% of the new technology.[21]

New Technology Transitional Pass-through Payments in Hospital Outpatient PPS

Pass-through payments are based on 95% of AWP for the drug less CMS's estimate of hospital acquisition cost for the drug.

CMS uses hospital claims data to determine the relative weights and payment rates for ambulatory payment classifications (APCs) in the outpatient prospective payment system (OPPS). Certain new technology items, such as drugs, biologicals, and devices for which costs are not adequately represented in this claims data receive transitional pass-through payments in addition to the payment for the APC with which the new technology is associated. In order to be considered for a pass-through payment, a drug must be considered to have a cost that is "not insignificant" in relation to the APC payment for the procedures or services associated with the drug. Pass-through payments are made for at least two years but not more than three years, after which the hospital claims data for those new devices are folded into the applicable APC payment.

By law, total projected pass-through payments for calendar year 2003 are limited to 2.5% of total projected OPPS payments. Because pass-through payments are carved out of total OPPS payments to keep the program budget-neutral, each APC payment is reduced by 2.5%. For 2004 and subsequent years, CMS has the authority to set the pass-through at a percentage of the projected total payments up to 2.0%. If CMS estimates before the beginning of a calendar year that the total pass-through payments will exceed the limit for that year, CMS is required to impose a pro-rata reduction across all transitional pass-through payments to ensure that the limit is not exceeded.

For 2002, CMS incorporated some additional device costs into APCs associated with pass-through devices. This fold-in was an effort to reduce total pass-through spending. CMS estimated, however, that total pass-through spending still would exceed the 2.5% limit. Consequently, CMS imposed a pro-rata reduction of 63.6% for all pass-through payments including both drugs and devices from April 1, 2002 through December 31, 2002. For 2003, no pro-rata reduction was required. Many expiring pass-through drugs were folded-into base APC payments. To ease the transition and ensure proper payment levels, higher cost drugs will continue to be paid separately but at fixed amounts based on hospital charge and cost data (rather than based upon AWP).

[21] An example of the new technology special add-on payment can be found in the October 10, 2002 *CMS Health Care Industry Market Update: Medical Devices and Supplies* on page 18.

Average Wholesale Price

Average wholesale price (AWP) is a manufacturer-supplied price, not currently defined by any federal law or regulation, and is presently compiled by compendia such as the *Red Book*. Numerous studies have suggested that AWPs, as currently calculated, are higher than the prices drug manufacturers and wholesalers actually charge to physicians and other providers. Medicare beneficiaries are directly impacted by the AWP price of these drugs (except for flu and pneumonia vaccines) because they affect Part B premiums, the $100 Part B annual deductible, and the 20% co-insurance payment for drugs.

Under Medicare, drugs not paid under a prospective payment system are paid based on the lower of the billed charge or 95% of the drugs' AWP, a CMS-determined price identifier. These drugs include drugs administered incident to a physician's service, immunosuppressive drugs furnished by pharmacies, drugs furnished by pharmacies for use with durable medical equipment (*e.g.*, nebulizer drugs), covered oral anti-cancer drugs, and drugs other than erythropoetin that are not included under the end-stage-renal-disease (ESRD) composite rate payment.

For brand name drugs that have only one source, the payment is equivalent to 95% of the AWP for that product. For multi-source drugs, the AWP is equal to the lesser of the median AWP of all of the generic forms of the drug, or the lowest brand name product AWP. For purposes of payment, a "brand name" product is defined as a product that is marketed under a labeled name that is other than the generic chemical name for the drug or biological.

A recent General Accounting Office report states that Medicare payment rates in 2001 for Part B covered drugs were much higher than the actual acquisition costs for physicians and pharmacy providers. The report indicated discounts of 13% to 34% off AWP were common for many physician-administered drugs and were as high as 65% to 86% for two specific drugs.

A recent report by HHS Office of the Inspector General showed that of the $3.7 billion Medicare spent for 24 drugs in 2000, the program would have saved $1.9 billion if the drugs had been reimbursed at prices available at the Veterans' Administration (VA). If Medicare paid the actual wholesale prices for these 24 drugs, the program would have saved $887 million a year. For example, consumers can buy a monthly supply of albuterol from Internet pharmacies for around $63. For the same one-month supply, Medicare pays $120 (95% of AWP), which includes $96 payment from Medicare and $24 co-insurance from the beneficiary. The beneficiary's 20% co-insurance payment is greater than the VA's entire monthly payment of $17.50 payment.

The current AWP structure causes several problems for the current Medicare payment system. Because payments are currently tied to published AWP, Medicare cannot obtain the discounts for which private payors can negotiate. AWPs that overstate actual acquisition costs for drugs also result in higher outpatient PPS transitional pass-through payments for many drugs, potentially leaving less money available for other items eligible for pass-through payments under the limit. In addition, manufacturers can arbitrarily increase published AWP and, in turn, offer physicians or providers deeper discounts. This can create an economic incentive to choose particular treatments for Medicare patients, because the payment exceeds the cost creating a profit margin for the provider.

Supplemental Insurance for Medicare Beneficiaries

In 1999, 23.8% of Medicare beneficiaries lacked outpatient pharmacy coverage for the entire year. Beneficiaries most likely to lack drug coverage were those who lived in rural areas, were aged 85 and older, were near-poor (*i.e.*, individual income between $10,001 and $20,000), and had no chronic health conditions. In standard private-sector Medigap plans that cover drugs, drug benefits are capped and require a 50% co-pay and a $250 deductible. In March 2002, 13% of Medicare+Choice (M+C or Medicare managed care plans) enrollees had no drug coverage, 15% could elect drug coverage for an addition premium payment, and 72% had drug coverage in their basic plan (although the benefit was restricted to generics only in about 30% of cases). We show sources of prescription drug coverage for Medicare beneficiaries below.

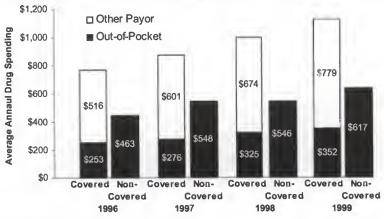
Figure 39: Sources of Prescription Drug Coverage for Medicare Beneficiaries

	% of Beneficiaries		
Source of Coverage	**1997**	**1998**	**1999**
Employer-sponsored	29.8%	30.5%	30.4%
Medicare HMO	11.0%	13.2%	15.4%
Medicaid	11.2%	10.3%	11.1%
Medigap	10.9%	10.6%	11.0%
Other public	1.9%	1.8%	1.7%
Switched coverage during year	8.0%	7.1%	6.6%
No drug coverage*	**27.2%**	**26.5%**	**23.8%**

Source: CMS, Office of Research, Development, and Information.
* Note: No drug coverage at any point during year.

Over 40% of Medicare beneficiaries in 1999 had private supplemental insurance that included a pharmacy benefit, although they may be subject to an annual spending cap. In 1999, the average Medicare beneficiary with drug coverage spent $352 out-of-pocket on prescription drugs, or 31% of his or her total drug costs. The average Medicare beneficiary without drug coverage spent $617 out-of-pocket on prescription drugs—and 45% less than the total drug spending of a covered beneficiary. These numbers are not adjusted for under-reporting and are shown in Figure 40.

Figure 40: Prescription Drug Spending by Medicare Beneficiaries



Source: CMS, Office of Research, Development, and Information. Data from the Medicare Current Beneficiary Survey (MCBS) 1996-1999 Cost and Use Files.
Note: Medicare beneficiaries may have drug coverage under employer-sponsored plans, Medicare+Choice, Medicaid, Medigap, or other public programs. Data are not adjusted for under-reporting.

Medicare-Endorsed Prescription Drug Card Assistance Initiative

On September 4, 2002, CMS published final regulations for Medicare endorsement of private prescription drug discount cards to become effective in 2003, although legal challenges by associations of pharmacists and chain drug stores opposed to the initiative could further delay implementation. Private insurance products regularly achieve manufacturer rebate and discounts between 2% and 35% on individual brand name drugs. The Medicare prescription drug card initiative hopes to educate and provide beneficiaries with the private sector tools used to lower prescription drug prices through group purchasing. Medicare endorsement of the drug discount cards is to assure that the programs meet certain requirements. The initiative also helps beneficiaries identify and use cards that provide other valuable services. As an additional benefit, it gives seniors and people with disabilities much-needed experience with choosing formularies and other prescription services that would likely be an integral part of a competitive prescription drug benefit in Medicare. The card is not intended to be a substitute for a Medicare drug benefit, but will educate beneficiaries about the private sector tools used to lower prescription drug prices in plain and simple terms, and will provide assurance that the Medicare-endorsed drug discount cards meet certain minimum requirements. This initiative will educate beneficiaries about the tools available to reduce prescription drug costs by officially endorsing those discount cards that meet the requirements.

Once the program is operational, seniors and people with disabilities will be able to enroll in only one Medicare-endorsed card program at a time. An incentive to compete for enrollment will encourage card sponsors to secure and pass through to beneficiaries the highest possible manufacturer rebates and discounts. Beneficiaries will pay no more than a $25, one-time fee at enrollment. Competition for enrollees will provide incentives for card sponsors to reduce fees even further. Beneficiaries will have the option to switch cards every six months (but may have to pay an additional enrollment fee). Card sponsors must publish discounted prices, and under the initiative, reliable, easy-to-compare information will be provided to allow beneficiaries to choose the discount card program that best meets their needs. All sponsors must provide an extensive national or regional networks of retail pharmacies, and sponsors are encouraged to adopt quality-enhancement tools of private drug benefit plans, including education, monitoring and prevention of adverse events, and pharmacy counseling services.

Medicaid

Medicaid, the federal-state partnership program that pays for health care services for certain groups of low-income persons, covered 42.3 million Americans in 2001 and spent about $20 billion on drugs (after subtracting rebates). All states elect to offer outpatient prescription drugs in their Medicaid programs. From 1998 to 2000, drug costs were the fastest growing component of Medicaid expenditures, growing an average annual rate of 20%, compared to overall Medicaid expenditure growth of 9%. To slow this growth rate, states are pursuing a variety of cost containment methods including reducing payment, seeking supplemental rebates, requiring generic substitution, establishing preferred drug lists (PDLs), and requiring prior authorization of drugs.

The Medicaid Drug Rebate Program requires drug manufacturers to pay rebates on drugs reimbursed by Medicaid. The drug manufacturer must also enter into discount pricing agreements with the Department of Veterans' Affairs and other covered federal entities to have its drugs covered by Medicaid. The mandatory federal Medicaid rebate for brand drugs is the greater of 15.1% of the average manufacturer price (AMP) per unit or the difference between the AMP and the best price per unit. "Best price" is the lowest price offered to any purchaser in the United States, and includes price reductions due to cash discounts, free goods, volume discounts, and rebates. The mandatory federal rebate for generic drugs is 11% of the AMP per unit.

Federal regulations require that each state's reimbursement for a brand name or certain other drugs not exceed the lower of estimated acquisition costs or the providers' usual and customary charge to the public for the drug. Payment for multiple source drugs which meet certain criteria cannot exceed the federal upper-limit (FUL), an amount determined by CMS. FULs are determined for drugs that have a certain number of therapeutic equivalents, and have at least three suppliers. Drugs without FULs, such as single source brand drugs, are reimbursed at the estimated acquisition cost (EAC) of the drug—typically determined by state agencies as a percentage discount off AWP. States are also required to pay a dispensing fee.

The Department of Health and Human Services' Office of the Inspector General estimated that states paid an average 10.3% discount to AWP for all brand and generic drugs that are not on the FUL drug list in 1999. The study also found that the actual pharmacy acquisition cost for single source brand drugs was 17.2% below AWP, for all drugs without FULs 27.2% below AWP, for multiple source brand drugs 24.4% below AWP, for multiple source non-brand drugs 54.2% below AWP, and for multiple source drugs with FULs 72.1% below AWP. The report concludes that the current method of reimbursing for drugs using a single percentage discount does not adequately consider the large fluctuations in actual prices between brands and multiple source drugs.

As of December 2002, 27 states have operational programs that provide outpatient drug assistance for some low-income groups that do not qualify for Medicaid; another six states have enacted laws that have not been implemented. Although programs vary, all programs cover the elderly population, and some also cover the disabled and those with specific chronic illnesses.

SUMMARY

- Despite recent generic competition and a slowdown in new product flow, which caused some margin deterioration, the branded drug industry enjoyed a strong 20% average profit margin in 2001.

- While industry spending on research and development has been increasing, some analysts noted decreased productivity as fewer new drugs are being approved.

- Drug companies can maximize current drug franchises by developing new versions of existing drugs (*e.g.*, Claritin/Clarinex and Prilosec/Nexium).

- The generic drug industry has benefited from patent expirations on branded drugs and managed care cost-containment efforts to increase generic use. Generic drug companies posted a 16% average profit margin in 2001.

- Although most biotechnology companies are unprofitable, the eight major profitable biotechs had a 24% average profit margin in 2001–slightly higher than that of the branded drug manufacturers.

- Over the past five years, all three sectors have outperformed the S&P 500. Drug makers are able to raise capital in the public equity and debt markets and many generate strong cash flow to finance capital needs. Venture capital financing for biotechnology remains relatively strong compared to other industries.

- While the pharmaceutical industry faces regulatory hurdles such as FDA approval and governmental coverage decisions, it also receives patent protection, other forms of market exclusivity, and significant R&D tax incentives.

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